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Archives of Internal Medicine

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INTERPRETATIONS OF THE INITIAL PHASES OF THE ELECTROCARDIOGRAM WITH SPECIAL REFERENCE TO THE THEORY OF "LIMITED POTENTIAL DIFFERENCES" *

SIR THOMAS LEWIS, M.D., F.R.C.P.

LONDON

The subject chosen for this lecture is one on which much has been written in recent years, but upon which there is still no complete consensus of opinion. In a review [1] written about three years ago I attempted to explain the constitution of the electrocardiogram on a new basis and put forward views of a novel kind. These views have been accepted by a number of workers; from other workers they have received criticism, publicly or privately expressed. The lack of uniform conclusions, I think, results largely from misunderstandings, such misunderstandings as may be expected to arise when the subject discussed is not only intricate but concerned with the ultimate processes of cellular activity and its manifestations. In studying the electrocardiogram we attempt to explain its general deflections in rational terms, yet the terms which we are forced to employ are terms which refer to intimate and intangible effects of cellular physics and chemistry. Although, as may be acknowledged at once, I have experienced recurring difficulty in my attempts clearly to conceive the manner in which the electrical events are related to events in the muscle; yet the conception at which I arrived some few years ago and which is now reconsidered in the light of recent discussion and observation has not altered fundamentally, though it may, perhaps, have grown a little clearer during the interval. In attempting a more distinct statement of the case it seems desirable to state that while I refuse to stand committed, once and for all, to these views, yet our present knowledge does seem to necessitate movement from the older hypotheses in some such direction as will be indicated.

In discussing the question before us one rule stands out as paramount in importance; the facts and the hypotheses must be divided from each

* Seventh Mellon lecture.

* Working on behalf of the British Medical Research Council at University College Hospital Medical School, London. Delivered before the Society for Biological Research, School of Medicine, University of Pittsburgh, May 8, 1922, and before the California Academy of Medicine, San Francisco, 1922.

1. Lewis: The Mechanism and Graphic Registration of the Heart Beat, London, 1920.

other as scrupulously as possible. Hypothesis cannot be avoided, perhaps never will be avoided, in a full consideration of our problem, and it would be presumptuous if my views were brought before you as views approaching to a final solution. Nevertheless, by carefully weighing our present knowledge, certain final statements may be made, certain statements may be denied, and we can bring our conceptions a step

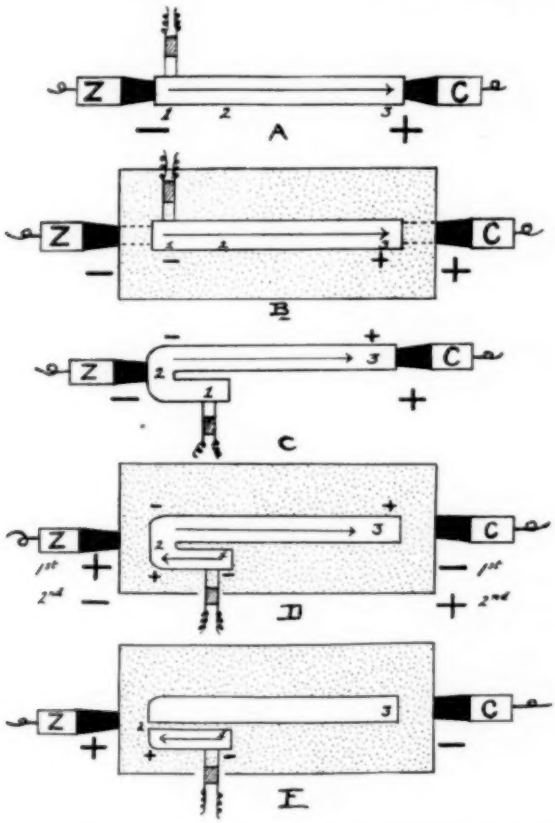

Fig. 1.—Diagrams, illustrating the potential differences in simple muscle strips, activated at one end.

nearer clarity and truth. Of one thing I feel sure, namely, that a close consideration of the views expressed, and further observations tending either to support or to destroy them, will prove fruitful.

In considering the meaning of the electrocardiogram, we have all started from a common basis. By common consent, if you place two leading-off electrodes directly on the two ends of a narrow strip of

uninjured muscle (Fig. 1 A) and now stimulate the muscle to contract in the region of one contact, the galvanometer shows the development of a difference in potential between the two contacts, that which lies at the point stimulated (Z) becoming negative relative to its fellow (C). The galvanometer shows us that an electromotive force is developed between these two points; current flows from one to the other through the muscle and through the galvanometer. This experiment, easily performed, has been carried out by very numerous observers with uniform results; the same event is witnessed whether voluntary or cardiac muscle is used, but it is the last only which I shall ask you to hold in mind during this lecture, for it is on cardiac muscle alone that I feel competent to speak, and in respect of which alone I shall draw my conclusions. It is on this experiment that the conclusion, which we have all accepted, is based, namely, that cardiac muscle entering the active state shows relative negativity to muscle which is inactive. But although this observation is easy to confirm, and although the conclusion derived from it does not seem open to question, I believe that it often gives rise to misconception when the meaning of the electrocardiogram is considered in the light of it.

The way in which the chief misconceptions arise I will endeavor to explain ultimately. Meanwhile, it should be remarked that in the simple experiment described the electrodes are placed against very small areas of the muscle strip; this method of leading chiefly signals the events which occur at the ends of the muscle, rather than the events in its whole length. Further, it is to be noted that when a difference of potential arises between the two ends as a result of activity of one end, the current flow is necessarily confined to the line of the muscle; for the muscle is isolated. The line of the muscle represents the line of the electrical axis, or the line of maximal potential difference.

Let us now take a second example (Fig. 1 B), one which, in the simple form illustrated, is theoretical, but one which would be more comparable to the experiment of electrocardiography. Imagine a strip of cardiac muscle completely embedded in a moist conducting substance, and that our contacts are placed, not immediately on the ends of the strip, but on the substance in which the muscle lies embedded. So they lie in human electrocardiography. If now the muscle end 1 becomes active, the galvanometer will again record current flow. The muscle end 1 we know becomes relatively negative to the muscle end 3; the contacts Z and C will no doubt reflect this change. If you wish to do so you may regard the contacts as prolonged through the medium in which the muscle is embedded, to the nearest points of the muscle, *i. e.*, to the original ends 1 and 3. There is this contact, but it is not the sole contact, for our electrodes are now connected, not only to the ends of the muscle, but to its whole surface. This difference

between the two methods of leading off should not influence the direction of the first potential difference exhibited by contact *C* and *Z*, when, as in our illustration, we are dealing with a straight and narrow strip of muscle lying in one line between the contacts; but as we shall see, it becomes of consequence when the relation of muscle to contacts is altered. A second difference between the two methods of leading off is also to be noted. When, in the last experiment, the muscle is embedded in a conducting substance, the current flows not only through the muscle and galvanometer; it flows through the surrounding medium. In other words, we have introduced a series of shunts along the borders of the muscle and these decrease the amount of current flowing through the galvanometer. While we may expect the movement of the galvanometric recorder to maintain its original direction (contact *Z* showing relative negativity to contact *C*), we may not expect its movement to be so considerable.

I emphasize the fact that the comparison made is between an actual experiment (Fig. 1 A) and a theoretical experiment (Fig. 1 B). The actual events in the second experiment (Fig. 1 B) have, I think, not been recorded, though there is sufficient evidence based on observation of a less direct kind to convince us that the curves obtained in the first and second experiment will have the same general form in their initial phase. That there will be this smilarity is, I think, generally recognized; it is not a matter in dispute. But this conception is apt to lead up to a second, namely, that curves taken by the two methods are built up in identical fashions; and that the two methods of leading will in all circumstances yield similar results. They may do so when a simple and narrow strip of muscle is placed in line with the leading off contacts; but they do not, I believe, in all circumstances. Suppose that the unembedded muscle is bent on itself at one end and that the contacts are placed at *2* and *3* (Fig. 1 C). Again, there will be agreement as to the effect produced. Soon after 1 is stimulated, a current will flow through the galvanometer in the original direction, indicating that contact *Z* has become relatively negative to *C*. This change is set up when the muscle on which contact *Z* lies becomes active. It is not produced by activity of the muscle strip between 1 and *2*; activity in this portion of the muscle has no material effect since the free end 1 is not connected to the leading off contact *C*. This illustration serves to emphasize the fact that when contacts are placed directly on the muscle, that it is an event occurring in the muscle immediately under the proximal contact which is responsible for the first swing of the recording instrument.

We come next to the fourth and crucial example, the muscle bent on itself and embedded (Fig. 1 D). In these circumstances how will the current first flow? I have asked this question of many physiologists

during the past six years, and have obtained almost always the reply that the direction of current flow will be the same as in the last example. It is said that 1 will become negative relative to 3, and that consequently *Z* will show negativity relative to *C*. Now, this reply is an assumption ultimately based on the belief that the two methods of leading off are sufficiently similar; actually the experiment has not been performed in this simple form. For a long while I have felt unable to accept this view of what will happen. The view is inconsistent with certain experiments which will be described presently. The view which I put forward is that relative negativity will first develop at contact *C*; and it will develop at *C* because, when 1 becomes active, we are leading off from the embedded strip of muscle 1 to 2, and the remainder of the strip 2 to 3 does not for the moment concern us. It does concern us of course when the excitation wave in traveling along the strip moves into the region between 2 and 3; when the wave in traveling has turned the corner, *Z* will become relative to *C*, the flow of current becoming in consequence reversed. But for the moment we shall do well to concentrate attention on the first phase of the reaction, for this is in dispute.

The statement just made in respect of the first phase, brings us I think to the critical arguments of the discussion, namely, does the prolongation of the strip from 2 to 3 effect the reaction shown by the galvanometer when 1 becomes active. The usual view has been that it will. My own view is that it does not.

You may ask, why the actual experiment is not performed? The reply is that it cannot be carried out in so simple a fashion on cardiac muscle which is uninjured, and that if you use injured muscle, your experiment is open, on theoretic grounds, to serious criticism. But, as I hope later to show, the experiment can be performed under somewhat more complex conditions, and that it yields the results which I anticipate.

The argument turns as stated on the influence or noninfluence of the portion of muscle 2 to 3, on the initial electrical reaction. According to one view, that which seems so far to have obtained the greater number of direct or indirect supporters, you are to consider 1 as relatively negative, and to consider the whole of the remainder of the muscle as relatively positive. This view implies that in determining the direction of flow, you are to join the center of the active mass of muscle to the center of the inactive mass. According to the other view, you are to consider the part of the muscle which is becoming active as relatively negative, and the inactive muscle in union with it and in its immediate vicinity as relatively positive. I put forward this second view because it is consistent with and explains my experiments and because so far as I am aware it is inconsistent with no other experimental facts; the first view, though it is admittedly consistent with many experiments, is

not consistent with all. For the sake of brevity we may term the first hypothesis that of "distributed potential differences," the second that of "limited potential differences."

At this point it may, perhaps, be appropriate to allude to my previous review. You will perceive that, if the hypothesis of limited potential differences is correct, the direction in which the current sets in the muscle will be the direction in which the excitation wave is at that moment traveling, for it will always move from the point which is becoming active to inactive muscle in the immediate vicinity of the latter. This association, which I believe to be an absolutely constant one,[2] is one on which I have laid stress; in doing so I have tended to imply that the first is dependent on the second. Such has not been my meaning though it has been inferred from what has been, perhaps, an unfortunate phraseology, and this inference is perhaps chiefly responsible for misconception of my hypothesis. To state that the direction which the excitation wave takes in traveling governs the form of the corresponding curve,[3] cannot be considered fundamentally sound.

A more correct expression would be that both are governed by one series of events in the muscle, and in consequence are definitely associated. It has been a matter of descriptive convenience to associate these two phenomena, direction of movement and direction of current flow. But because the meaning may be inferred that one is responsible for the other, I shall endeavor to avoid this method of description in my subsequent remarks.

Returning to the question at issue, namely, the influence of outlying muscle on the electrical reaction, let us consider the case of two entirely separate masses of muscle (Fig. 1 E). Under this arrangement, if 1 becomes active, the contacts at *C* will become negative to the contact *Z*. Here no one argues that the presence of the inactive muscle strip 2 to 3 will influence the result, it becomes part of the moist substance in which the strip 1 and 2 is embedded. To illustrate this statement, take the example of complete heart block. When the auriculoventricular bundle is divided experimentally or by disease, the electrocardiogram records the independent activities of auricle and ventricle. Each chamber gives its separate curve, but the curves of one and the other fall in

2. I would here express the view that, unless the conditions are very simple, the direction in which the current is setting in a muscle strip as a whole is not to be ascertained with certainty from an examination of two small points of contact on its surface (as in Fig. 1A); but in my view it can be ascertained by the method of leading which Fig. 1B illustrates. When I say that the association between the set of current and direction of travel is constant, I wish to refer to direction of current as ascertained by the method of indirect leading (method of Fig. 1 B) and by this method only.

3. The phrase actually used in "The Mechanism and Graphic Registration of the Heart Beat," London, 1920.

varying relationship to each other. It is quite clear from such records that activity or inactivity, partial or complete, in one chamber has no influence on the shape or amplitudes of the electrical currents derived from the other (Fig. 2). Providing that we are dealing with separate masses of heart muscle, the electromotive forces set up in one chamber are not influenced by those set up in the other. The forces developed in the two chambers find full and individual expression; in explaining such curves we do not balance activity in one chamber against inactivity in the other.

In regard, therefore, to the illustration (Fig. 1E) we are safe in assuming that the activation of strip 1 to 2 at point 1 will yield an electromotive force having a certain direction and amplitude, independently of what is happening in the strip 2 to 3. How does this arrangement of the muscle fibers differ from that illustrated by Figure 1D.

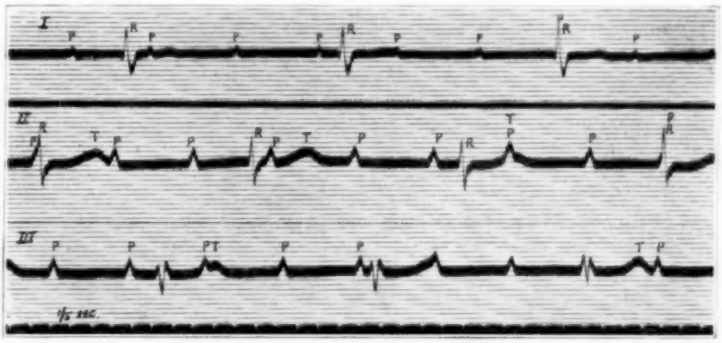

Fig. 2. Electrocardiograms from a case of complete heart block, and taken by means of Leads I, II and III.

In one respect only; in the first illustration there is functional union between the two strips at the point 2. If 1 is stimulated to activity in these two sets of circumstances, will the initial resultant swings of the galvanometer be in opposite directions; will they indicate relative negativity at *Z* in one case and at *C* in the other? According to the hypothesis of distributed potentials this will happen. But in both instances, when 1 becomes active, the strip 2 to 3 is recognized to be in a state of inactivity. The distribution of potentials is the same in both, unless we are to assume that when the two strips are part of one undivided piece of muscle, an active change happens in strip 2 to 3, rendering it relatively more positive to 1. In other words, if we are to accept the hypothesis of distributed potentials, it is essential to assume that, from its initiation, active change produced by stimulation does not confine itself to that end of the muscle which is stimulated. I know of

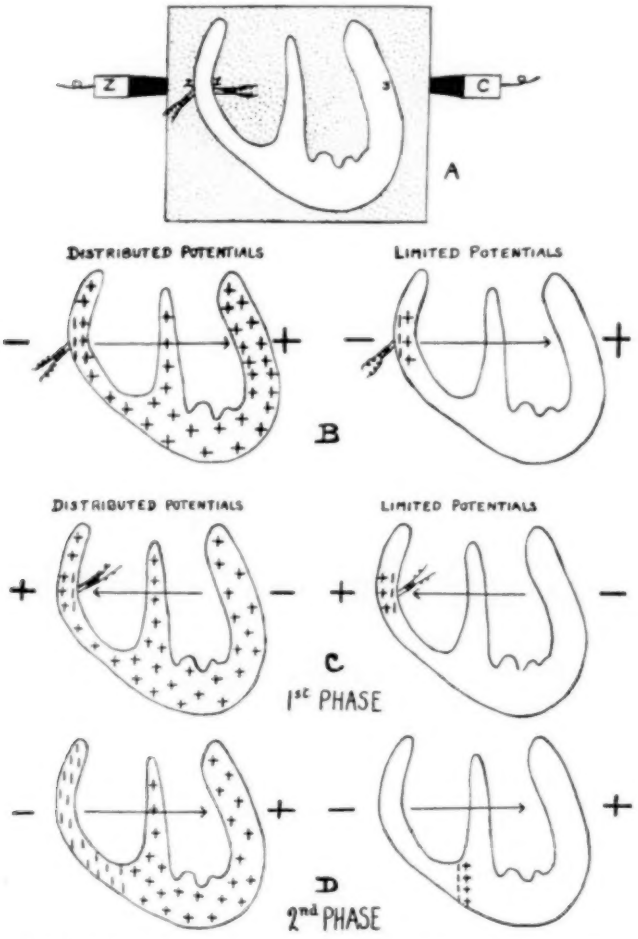

Fig. 3 A and B.—When the heart is stimulated at its epicardial surface (Fig. 3 B), contacts placed in line with the point stimulated show first of all an electrical relation which is indicated by the large + and — signs. This reaction of the contacts is explained alternatively by the hypotheses of distributed and limited potential differences (see small + and — signs of the diagram). In this example the distribution of potentials in the muscle and under the contacts is consistent, irrespective of the hypothesis chosen. A, C and D: The heart is stimulated at its endocardial surface and the potential difference recorded by the contacts is at first in one direction (phase 1) and later becomes reversed (phase 2). The supposed potential differences in the muscle, during the second phase, are consistent with what is found at the contact points, irrespective of the hypothesis adopted; but this is not so for the first phase; in this the hypothesis of limited potential differences is alone consistent with observation.

no evidence in favor of such a diffused effect; on the contrary, the argument based on the fact that in one instance we are dealing with a single piece of muscle and in the other case with separate pieces of muscle, though plausible, can be shown to be unsound. The experiment of the bent piece of muscle can be performed on uninjured heart muscle. It is accomplished as follows: Leading off contacts are placed on a dog's chest wall (Fig. 3A), the one on the right side, the other on the left, and the right ventricle is stimulated first on its epicardial surface at *2*, and secondly on its endocardial surface at 1, the points stimulated being in the same line as the leading off contacts. It will be obvious that, when we stimulate at *2*, the excitation wave will move in a general direction in the body from right to left across the heart (from *2* toward *3*). It will be equally obvious that if we stimulate at 1 the excitation will at first move in a general direction from 1 toward *2*, and that a little later the general course from *2* toward *3* will be pursued. In the

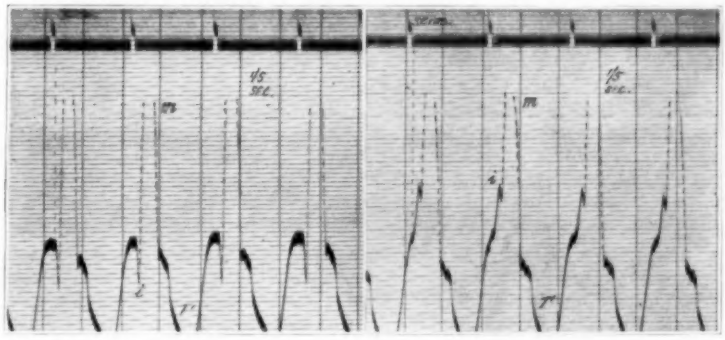

Fig. 4. An example of the findings of four distinct experiments. The lead was from the right chest wall (*Z* contact) to the left chest wall (*C* contact) and the wall of the right ventricle was stimulated on its epicardial surface (right hand record), and on its endocardial surface (left hand record). In the last case a small pair of long insulated electrodes was introduced through a small slit in the wall of the conus or through the jugular vein. The two points of stimulation (inside and outside) lay no more than 0.5 cm. from each other. The curves differ in one respect, the left hand curve begins with an initial phase *i* directed downward, in the right hand curve this phase is directed upward. These initial phases of the curves correspond to involvement of the wall at the point stimulated (the involvement being in opposite directions in the two circumstances). The main deflection *m* is similar in both curves; it represents spread from right to left in the ventricles as a whole. Curves of this kind are obtained most successfully if the lungs are well inflated so that good contact is maintained between the sides of the heart and the chest wall. The curves represent responses to rhythmic break shocks (single shocks give similar effects). The stimulus is recorded electrically in the top line. The curves are not distorted by the stimuli, as the time relations of stimulus and shock show; reversal of the direction in which the stimulus entered the heart did not affect the form of the curves.

first case the general direction in the body will be from right to left throughout the whole excitation of the ventricle; in the second case, it will be for a brief period from left to right, and eventually from right to left. The experiment affords the general condition illustrated by the straight and bent muscle strips of Figure 1B and D. The result of this experiment is instructive. Stimulate the epicardial surface and, from the first, contact *Z* is negative to contact *C*. This finding is consistent with both hypotheses, the potentials being distributed as shown in Figure 3 B and in Figure 4. Stimulate the endocardial surface (Fig. 3 C and D) and the curve has two opposite phases, a short first phase during which contact *C* is negative to contact *Z*, and a longer second phase during which contact *Z* is negative to contact *C* (Fig. 4). This finding is consistent with one of our hypothesis only, namely, that of limited potential differences. The association between the set of the current and the direction in which the excitation wave moves will be noted in this illustration. It constitutes a single and new illustration of an association which I believe to be firmly established and of which numerous examples have already been published.[5] It was because I found this association constantly to exist in the normal heart beat of amphibians, reptiles, birds and mammalia, classes in which the spread of the excitation wave is very diverse, that I first recognized the hypothesis of distributed potentials to be untenable, for it is inconsistent with this association, as the diagrams clearly show (Figs. 3 C and D).

It may suffice at the present time if a few of the simpler illustrations are cited. The first of these permits the display of some important fallacies. It is the instance of the normal amphibian heart beat. The amphibian heart (Fig. 5) comprises not only sinus, auricle and ventricle, but also a bulbus arteriosus. It is on hearts of this or of a closely allied type, that almost the whole of the preliminary explanations of the electrocardiogram have been based; and it is with the mistaken interpretation of these curves, and the hypotheses derived from them, that we have today chiefly to contend. In this early work the heart was examined by placing on the base and apex of the ventricle two contacts and connecting them to a galvanometer. Because in such curves as were regarded to be typical, the first deflection indicated relative negativity of the base, it was concluded that the base first becomes active; it was further concluded that the excitation wave spreads as a simple wave from base to apex. Now, further and closer observation by modern

4. In stimulating the epicardial surface the curve is not usually expressed as a single phase. It rises a little, hangs or falls away as the endocardial lining is approached, and then rises steeply to yield the chief deflection which represents rapid involvement of a large mass of the ventricular substance.

5. Phil. Tr. Roy. Soc., B. **207**:221, 1916.

methods has shown that the first of these conclusions is usually incorrect, and that the last conclusion is never true. These early observations on the cold-blooded heart and the conclusions derived from them are open to serious criticism. The direction of the first deflection does not, in point of fact, always indicate primary negativity of the base. The direction depends largely in a given animal on the point chosen at the base for examination; there is also much variation from animal to animal. Later observations have shown that sometimes a basal point is active before the apex; sometimes it becomes active after the apex (Fig. 5); sometimes certain points at the base are activated before, and certain points after, the apex. In all cases the base and apex are activated within a very short time interval of each other. The excitation first reaches the surface of the heart at neither base nor apex, it reaches

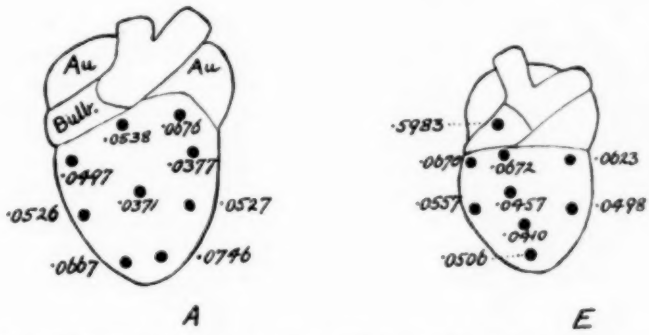

Fig. 5. — Outline diagrams of the hearts of *Bufo vulgaris major*, showing a number of surface readings expressed (in decimal points of a second) to the beginning of *R* in an axial lead. Toad A, an unpublished figure, showing that the base is activated earlier than the apex. Toad E (after the original figure) showing that the apex is activated earlier than the base. In both cases the central region of the ventral surface is activated earliest of all. In the axial electrocardiogram of each animal the chief deflection was an upright *R*; in the case of toad E, the electrocardiogram also showed a prominent *S* wave.

the central portions of the ventricle (Figs. 5 and 6 A) and races simultaneously up to the base and down to the apex; the race may be won in one other direction; usually it is won at the apex. It is easy to understand why these base-apex curves of early days often seemed to indicate primary negativity of the base. The extreme base does become active a little before the apex in some amphibian hearts, though that is not the rule. If the extreme apex is chosen for one contact, and a point somewhat removed from the base is chosen for the second, and this would be the natural tendency [6] of experiment, primary negativity

6. The tendency being to allow an interval of lesser or greater extent between the contact and the *A-V* junction.

of the base would usually be manifested; for the reason that a point a little removed from the base is usually activated earlier than a point at the extreme apex. The precise time relations of basal and apical activity being unknown beforehand, this observation would naturally be construed as indicating that the excitation wave starts at the base. From this conclusion, false as it was, it was an easy step to the still very prevalent general erroneous assumption that when, as is the rule, the basal contact of an indirect lead (method of Fig. 1 B) first demonstrates negativity, activity is confined to muscle which lies nearer to this basal contact than to the apical one. Thus, in human electrocardiography it has frequently been assumed that *R*, the chief deflection, is essentially a basal effect and that *S* is essentially an apical effect; for *R* represents relative negativity of the basal and *S* of the apical contact. Neither conclusion is justified.

These assumptions, erroneous as I believe them to be, arise chiefly from the idea that if muscle at the base is active, the basal contact will show relative negativity and, conversely, that if the apex is active, the apical contact will show relative negativity. These are views based on the hypothesis of distributed potentials. A primary basal activity may display itself in relative negativity of the apical contact as the experiment illustrated in Figure 3A clearly indicates. The erroneous assumptions also arise, in part, because the base-apex curve of the amphibian, where contacts are laid directly on the heart, has been assumed too rigidly to be comparable with the curves from outlying contacts such as are used in clinical electrocardiography. The difference between the two methods is that in the first the curve chiefly expresses the potential differences between two small areas, one at the base and one at the apex; while in the clinical method the lead (when axial) is from the whole of the basal and the whole of the apical parts of the heart; the clinical curves express the electrical changes in the entire mass of cardiac muscle; the direct leads do not. The two methods are strictly speaking incomparable (compare Figs. 1C and D from this point of view).

The axial electrocardiogram of the amphibian heart (Fig. 7), in so far as it expresses spread of the excitation wave, consists of the following deflections.

1. A chief and primary deflection (*R*) indicating relative negativity of the contact beyond the base.

2. An inconstant second deflection (*S*) indicating relative negativity of the contact beyond the apex.

3. A deflection (*B*), occurring at a late phase of the electrocardiogram, corresponding to activation of the bulbus arteriosus, and indicating relative negativity of the apical contact.

Let us deal briefly with the last deflection first. This bulbus deflection is due to the activity of muscle lying at the base of the ventricle; yet its direction indicates relative negativity of the apical contact. This observation clearly warns us against lightly concluding that relative

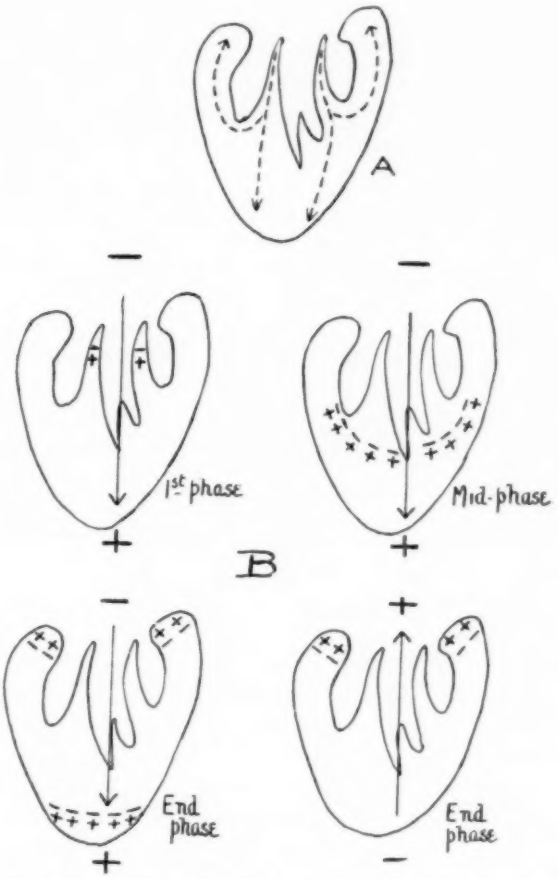

Fig. 6.—Course of excitation wave in activation of ventricle.

negativity at the apical contact necessarily means activity of the muscle lying nearer to the base than the apex of the ventricle. The direction of this deflection is what it is, because the excitation wave begins in the lower part of the bulbus (i. e., toward the apical contact) and the inactive muscle in its vicinity lies above it (i. e., toward the basal contact).

The position of the bulbus, relative to the rest of the ventricular muscle with which it is in functional union [7] does not affect the direction of the deflection.

Consider now the initial deflection (R) or deflections (R and S). The meaning of R according to my hypothesis is not obscure. It is due to set of the current in the axis of the heart, *i. e.* from above downward, over the greater part of that phase of the cycle during which the ventricle is becoming activated. The ventricle is activated in the gross from above downward. The excitation wave starts in the muscular funnel and trabeculae within the heart (Fig. 6A) and is at first propagated wholly in a downward direction. Actually the greater part or entire upstroke of R is written before the excitation wave appears at any point on the surface of the ventricle. To regard R as an evidence of general basal activity is obviously inconsistent with this observation; R corresponds to the activity of muscle lying deep inside the

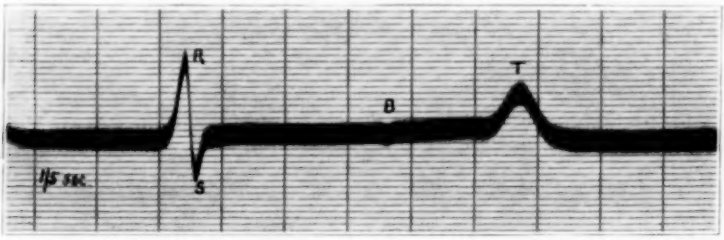

Fig. 7.—An electrocardiogram taken from a toad's heart; leading from the mouth and abdomen in the axis of the heart. The deflection produced by activity of the bulbus arteriosus (B) is directed downward.

central portions of the heart. The hypothesis of limited potential differences applied to the amphibian ventricles provides us with a clear conception of the electrical events, a conception which is consistent with the manner in which the excitation wave has been shown to spread. During the early phases of R's inscription the muscle is becoming active in the central trabeculae, this region is relatively negative, the relatively positive region lies apexwards and in its immedate vicinity (Fig 6B 1st phase). As the excitation wave proceeds downward, the advancing border spreads laterally, but the balance of the potential differences manifests itself still in the same direction (Fig. 6B midphase). In its

7. The reply which has been made, that there is a natural line of block between the two chambers, does not appear to me relevant. They are united functionally by muscle fibers, the region of block being simply a region of slow propagation; if it is held that this region of slow propagation constitutes a line of complete separation from the standpoint under consideration, the burden of proving this lies with those who hold the view.

further progress the advancing border of the wave is not only proceeding toward the apex, but is now also traveling back in the lateral walls to reach the base (Fig. 6 B end-phase left-hand figure). Activity in the region of the apex still tends to maintain the electric axis from base to apex; the basal activity tends to set it in a contrary direction. But the effect of this basal activity is apparently insufficient to upset the average direction, which still remains from base to apex. The basal contact is throughout relatively negative to the apical contact. If, however, as often happens in the amphibian heart, the basal segments of muscle are the last supplied, this opposition of the apical effects is removed and the effect of basal activity then appears It manifests itself in the form of an *S* wave, a downward deflection indicating relative negativity of the apical contact. The axis of the electromotive force is now from below upward (Fig. 6 B end phase, right-hand figure).

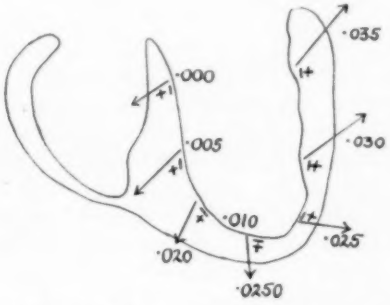

Fig. 8.—Times of arrival of excitation wave relative to each other indicated in decimal points of a second.

Thus, our hypothesis brings us to a reasonable explanation of a curious but actual observation, namely, that the appearance of an *S* wave in the electrocardiogram of amphibians is associated with late arrival of the excitation wave at the ventricular base. No other present day hypothesis will afford an explanation of this phenomenon. This example is in my view precisely comparable to that of the bulbus already cited. In both instances basal activities are responsible for relative negativity of the apical contact; but the present illustration has an advantage over the first, in that there can be no question here of separate muscle systems; the whole of the musculature of the ventricle is one uniform syncytium.

THE MAMMALIAN ELECTROCARDIOGRAM

Similar methods of observation are applied to the mammalian ventricle and, although in this instance we deal with a far more complex arrangement, similar correlations can be shown to exist between the manner in which the excitation wave spreads and the set of the elec-

trical axis from instant to instant. To consider the constitution of this electrocardiogram in full detail would detain us too long, it must suffice if by a single example I illustrate again the general principle of interpretation, and show that the hypothesis of limited potential differences is applicable in this case also. Let us take the simpler case, the excitation of the dog's left ventricle.

The excitation wave is found by observation to start in the septum of the ventricles; it is traced down the septum to the apex and from the latter up the lateral wall to the base. The times of arrival, relative to each other, are indicated in Figure 8 in decimal points of a second. But in moving along this semicircular path the wave does not proceed in a direction parallel to the borders of the muscular track, it is penetrating the wall in successive segments of its course; it moves always from within outward along centrifugal paths; each part of the wave travels from the endocardial to the pericardial surface. Throughout its passage, the electrical axis constantly changes so that, while in the initial stages this axis sits from left to right in the body, it gradually shifts to a base-apex direction; from this it swings more and more to the left until, eventually, and when the excitation wave is reaching the base of the left ventricle, the electrical axis is directed chiefly upward. This change in the direction of the axis is responsible for the complexity of the corresponding electrocardiographic curves. When the set of the axis is in the main downward, a basal contact (right shoulder) is relatively negative to an apical contact (left thigh); the corresponding upstroke in the electrocardiogram contributes to the formation of the well-known deflection *R*. On the contrary, when the set of the axis is mainly upward, the apical contact becomes relatively negative to the basal contact and the corresponding downstroke in the electrocardiogram is the chief constituent of the well known deflection *S*. As in the amphibian heart, *S* does not represent an apical activity, it represents a basal activity. Now this example, though complex, is a striking one. There is, within the reasonable bounds of error in observation, complete correspondence between the readings which indicate the distribution of the advancing excitation wave and the set of the electrical axis at corresponding phases of the cycle, when the set of this axis is read in terms of my hypothesis of limited potential differences. These observations are in full accord with our knowledge of the anatomy of the ventricle, in accord with a distribution of the excitation wave through the left division of the auriculoventricular bundle and its arborization; for the left division enters the ventricle on its septal surface and distributes its branches to the septum, to the apical parts of the heart and to the lateral walls of the heart and to the lateral walls at the base, in this order. Consider the ascertained order of spread and arrange theoreti-

cally the electrical axis, using the hypothesis of distributed potential differences, and one arrives at a result which is not consistent with observation. According to this hypothesis, relative negativity should appear, first of all, at the basal contact; secondly when the wave of excitation reaches the apex, the apical contact should appear relatively negative; finally when the wave returns to the base, the basal contact should again show relative negativity. The second and last suppositions are not in accord with the facts. But if, on the other hand, one arranges the potentials theoretically, using the hypothesis of limited potential differences, harmony exists.

In the light of these observations and in the light of those previously described, I have no hesitation in discarding the older hypothesis and in accepting in its place the hypothesis which I term that of limited potential differences. It is in accord, so far as can be seen, with all present observations on heart muscle. I do not claim that it affords a final explanation, being quite prepared to find that future observations will necessitate its modification; but it is desirable, nay it is essential, that we should possess ourselves of an hypothesis which harmonizes with all present day observation; an hypothesis which will serve to direct further experiment along fruitful channels. Hypotheses which are out of harmony with present observations will not serve this purpose. The present hypothesis has been put forward and is now emphasized in the belief that it will supply our present and immediate needs.

A CASE OF HODGKIN'S DISEASE TREATED WITH ROENTGEN RAYS FOR SIX YEARS *

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INTRODUCTION

Cases of Hodgkin's disease, involving the stomach or wall of the gut, while rare have been reported by various observers (Briquet,[1] Musser,[2] Wells[3] and Reiman[4]). The case reported by Briquet is of interest because it was the first of this type on record, and is accepted now as a case of Hodgkin's disease. Apparently in none of the cases referred to was there a perforation of the intestine.

Our patient was a young woman observed and treated with roentgen rays for six and a half years. Microscopic examinations were made before treatment was instituted, and, again, at the post mortem.

The course of the disease, type of temperature ("Rückfall"), blood findings and many of the physical signs and symptoms are similar to those frequently noted in this disease. The case is thought to be of interest for the following reasons:

1. Length of time the patient was observed and treated with the roentgen ray.
2. Apparent effect of the roentgen ray on the clinical course and pathology of the glands.
3. Type of temperature both early and late in the disease.
4. Termination due to perforation of the intestine.

REPORT OF CASE [5]

Clinical History.—F. M. (history No. 42181), white woman, aged 22, single, clerk, was first admitted to the Presbyterian Hospital in March, 1914.

Chief Complaint.—Pain in abdomen and weakness.

Family History.—Negative.

Past History.—Swelling of legs was treated by injections (?) three years ago. She had had frequent attacks of tonsillitis. Her menses were irregular; the last period, one month ago.

Present Illness.—Nine weeks ago she first noticed a tired feeling, insomnia and anorexia. For the past two weeks, she has had a burning pain in the left

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* From the Medical Clinic and Pathological Department of the Presbyterian Hospital, Columbia University.

1. Briquet: Cruveilhier's Atlas **2**: Pt. 34, 1835-1842.
2. Musser, J. H.: Tr. Assn. Am. Phys. **16**:638, 1901.
3. Wells, Gideon H.: Am. J. M. Sc. **128**:837, 1904.
4. Reiman, S. P.: Cleveland M. J. **15**:94, 1917.
5. This case is one of those referred to by Longcope and McAlpin in their article on Hodgkin's disease in Oxford Medicine.

side, radiating to her back. This pain has no relation to meals, but is worse at night. There is no vomiting, epistaxis or swelling of legs. She has lost 15 pounds in weight. Five days ago her temperature was 103 F.

Physical Examination.—The patient is a pale thin woman. The tonsils are ragged. The lungs are clear. The heart is negative, except for a soft blowing systolic murmur over the pulmonic area, which is not transmitted.

Abdomen: There is some tenderness on deep pressure one inch to the left of the midline and two inches below the umbilicus. There is no rigidity, no masses or signs of fluid. The liver and spleen are not palpable. Reflexes: Corneal, absent. Others, normal.

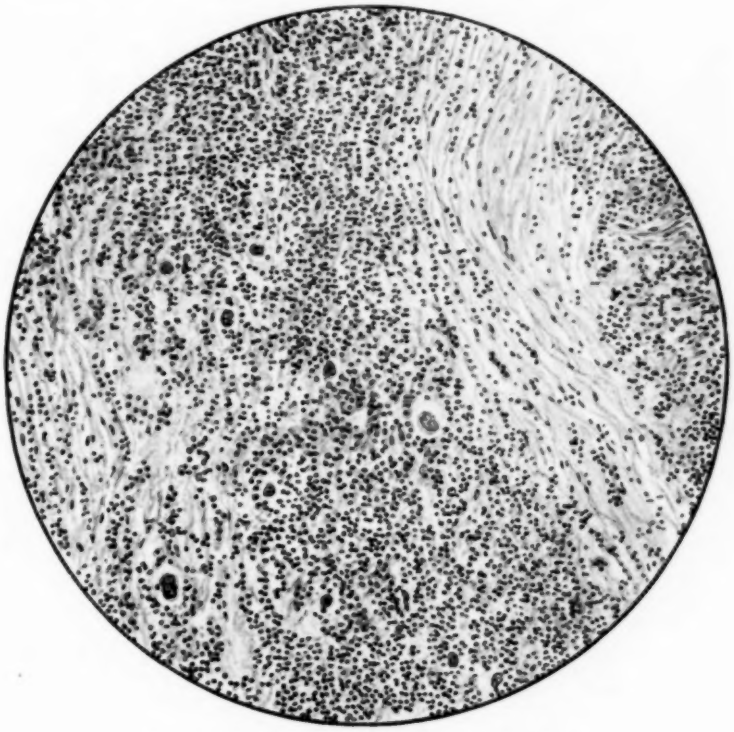

Fig. 1.—Hodgkin's disease. Mesenteric gland.

Gastric analysis on two occasions showed a low total acidity; no free hydrochloric acid; no lactic acid; a faint trace of blood. The blood Wassermann and the Pirquet test were negative. Tuberculin and intradermic tuberculin tests were negative. Urine: Negative, except for occasional trace of albumin; no casts.

Clinical Course.—Twenty days after admission, a hard, irregular, freely movable mass was felt in the right lower quadrant. It was not tender and there was no rigidity. Percussion over the mass elicited tympanites. Roentgen-ray examination of the abdomen was negative for glands.

Roentgen-ray examination of chest: Throughout the right lung and at apex of the left lung are shadows suggestive of tuberculosis.

The abdominal mass gradually increased in size, and April 18 an exploratory laparotomy was done. There were numerous enlarged glands in the mesentery of the hollow viscera. Some of these measured at least 5 cm. in diameter. There were three main masses rather loosely connected and more or less distinct from each other. These were in the mesentery of the ileum and jejunum. The lowest was in the ileocecal angle. The next one lay about over the vertebral column, while the third was well up near the duodenojejunal angle. There were numerous discrete glands beneath and behind the cecum; small nodules, 0.5 cm. in diameter, were also scattered in the mesentery. These appeared to be yellowish in color and cheesy.

Pathologic Report (15593).—Mesenteric gland. Gross: Nothing characteristic was noted. Microscopic: Capsule thick and fibrous. Major part of mass consists of lymphoid tissue. Stroma is a fine reticulum. Scattered through this are small round cells and eosinophils, also many cells of the Dorothy Reed type. Evidently, this is a case of Hodgkin's disease, fairly well advanced (Fig. 1).

The wound healed promptly. Later thrombosis of the left internal saphenous vein developed. Pain in the lumbar region was relieved by morphin and paraldehyd. The temperature which had been 101 and 102.8 F., gradually came down. She gained 9 pounds in weight. The mass in the abdomen remained the same. No superficial glands were ever palpable. The heart and lungs were as at the previous examination. Blood pressure was 100/64 and 90/80. Discharged, June 19, 1914.

Interval History.—She was admitted to the General Memorial Hospital, July 7, and discharged July 10, 1914. There was tenderness in the epigastrium. A few nodules, size of a hazel nut, were found in the right iliac region, which was the first time that a superficial gland was ever palpated. The spleen and liver were palpable. Roentgen-ray therapy was begun July 24, 1914. Between the first and second treatment one month elapsed. The patient felt better after treatment. Later the roentgen-ray treatments were given every two weeks.

Second Admission.—Nov. 14, 1914. Three days before admission she had severe abdominal pain, with vomiting and slight fever. At this time, the general appearance of the patient was improved. A large, hard, nodular mass was felt in the abdomen, extending from the ensiform to the umbilicus, and 3 cm. to each side of the midline. It moved with respiration and was slightly tender. No definite mass could be made out in the right lumbar quadrant, but an indefinite sense of resistance was noted. The liver, spleen and kidneys were not felt. Cervical, axillary and inguinal lymph nodes were not palpable. The skin was negative. The eye grounds were normal. Wassermann: negative.

Later is was impossible to definitely outline the abdominal mass and most of it seemed to be to the right of the midline. Other smaller masses felt in abdomen.

She had dull aching in the back, radiating about the waist. Temperature gradually rose to 103.2 F. Pain was quite severe and not relieved by fairly large doses of morphin. There followed gradual improvement and the temperature became normal.

Blood cultures (Rosenow deep tubes): Sterile.

Roentgen-Ray Examination (Roentgenogram 31424).—Slight increased diffuse density of lungs. Shadow about roots unusually strong. Left diaphragm slightly irregular with bulging over the spleen.

Discharged, Dec. 22, 1914, somewhat improved.

Interval History.—She was given roentgen-ray treatments at somewhat irregur intervals.

March 1, 1915: Deep in both inguinal regions are glands about 2 cm. in diameter. None palpable elsewhere. Abdominal mass much smaller and much less distinct.

Sept. 21, 1915: Several enlarged glands in the left supraclavicular fossa formed a mass 6 cm. in diameter and about 2 cm. thick. These glands decreased

in size under roentgen-ray treatment. Abdomen: Slight resistance just below costal arch in midline, with indefinite sense of a mass which cannot be mapped out.

She has had periods of fever. One of these lasted twenty days, and the temperature went as high as 103.2 F.

In December, 1916, she showed signs of hyperthyroidism — nervousness, diarrhea, insomnia, palpitation and tremor, but no exophthalmos. These symptoms gradually improved during the next two years. Roentgen-ray treatment of glands was continued during this period.

June, 1918: Menses irregular; some loss of weight; temperature elevated two or three degrees each night. Abdomen is somewhat distended; sense of mass made out along median abdominal line. Spleen not palpable. Some retrosternal dulness. Right femoral nodes enlarged.

Jan. 31, 1919: Abdomen a little full and resistant, but no mass distinguishable. Inguinal nodes about 3 by 4 cm. in diameter.

April 25, 1919: Abdominal masses faintly palpable. Spleen felt 8 cm. below costal margin, hard and firm. No masses in neck.

Third Admission.—June 2, 1919. Since attack of influenza eight months ago, she has not been as well as before, and has lost 20 pounds in weight.

Physical Examination. — Deep and superficial lymph nodes above the left clavicle are enlarged. The inguinal lymph nodes are enlarged, firm and smooth. Spleen is palpable four finger-breadths below the costal margin.

June 18, 1919, she was given by transfusion 450 c.c. blood, followed almost immediately by a severe chill (Chart 3).

During most of her stay in the hospital, the temperature was between 100 and 103 F., but finally it came down to normal. She was given four roentgen-ray treatments which were followed with some reaction (Chart 3). Her general condition gradually improved, and she was discharged June 27, 1919.

Interval History.—July 16, 1919: Tenderness over spleen; signs of mediastinal mass.

September 11: The patient returned to the dispensary complaining of abdominal pain, obstinate constipation, chills and fever. She has had six roentgen-ray treatments since her discharge June 27, 1919. After each treatment she had general malaise, sick headaches, fever and nausea.

Fourth Admission.—Sept. 11, 1919. She has had a gnawing pain in the back, not affected by respiration. Temperature was elevated in the evening, low in the morning. The pain in the splenic region was made worse by respiration. Constipation increased this pain. Constipation was very obstinate and not relieved by medication which made the pain worse. The fever has lasted over periods of from three to five weeks, with afebrile intervals. The febrile periods have been increasing in length. Fever accompanied by drenching night sweats.

Physical Examination.—Glands: One postcervical gland on the left side was firm and about the size of a peach stone. A few small glands were palpable in the right axilla. Abdomen: Liver, 2.5 cm. below costal margin. Spleen, 8 cm. below costal margin and 4 cm. to left of midline. Dulness extends up to fifth space. Spleen was hard and quite tender; moved freely with respirations. No other masses were felt in abdomen.

Clinical Course.—September 14, signs of fluid in the left pleural cavity were made out, and the next day 100 c.c. of yellowish turbid fluid was aspirated. Signs of fluid again appeared and October 14, 900 c.c. of turbid fluid was removed from the left chest. After the third transfusion (October 16) the patient's condition improved and the temperature came down to normal.

November 6: Left pleural cavity was aspirated, and 700 c.c. fluid was withdrawn.

November 30: The spleen was larger than previously; edge sharp, hard and irregular.

December 9: Left eye: Fluid vitreous was filled with opacities. Retina detached at lower part. Disk partly atrophic. Right eye: Patch of mild chorioretinitis found. Floating opacities in vitreous.

There were always signs of fluid in the left chest and at times also in the right chest. The patient complained frequently of pain in the right side of the chest and also in the splenic region. There was abdominal distention which was only slightly relieved by enemas, etc. The spleen was enlarged and tender. The temperature would be elevated for about two weeks, then descend gradually to normal and remain so for from ten days to four weeks, then rise again. During febrile periods, constipation was obstinate and there

Fig. 2.—Hodgkin's disease. Involvement of peritoneum.

was severe abdominal pain with distention. In the afebrile periods, she seemed to be much better. Because of weakness roentgen-ray treatments were discontinued after March 10, 1920.

After transfusions, of which she had nine, there occurred—with one exception—a sharp rise in temperature. Immediately after this rise the temperature went down rapidly to a lower level than it reached prior to transfusion. This drop in temperature was accompanied by improvement in general symptoms.

August 27 an operation for intestinal obstruction was considered but was not done because the patient was relieved by turpentine enemas given in the knee chest position.

September 25, she complained of gas in the intestines with cramps. The abdomen showed only moderate distention, and was soft and tender. Treatment was unavailing. She gradually grew weaker and died without reacting to stimulants.

Final Diagnosis.—Hodgkin's disease.

Necropsy Report (9061).—Anatomic diagnosis: Hodgkin's disease, with involvement of the spleen, liver, lungs, pleura, intestine and peritoneum; ulceration of colon; perforation of transverse colon; acute generalized peritonitis; left hydrothorax; fibrous pleural adhesions; chronic mitral endocarditis.

The body is that of a well developed, moderately emaciated white woman, 152 cm. in length. The mucous membranes are pale. Superficial lymph glands are not palpable. The abdomen is distended and tense. There is an old scar in the midline between the umbilicus and pubis. There is some edema of the feet.

Abdominal Cavity.—The abdominal cavity contained a considerable quantity of foul gas and 500 c.c. of thick, dark greenish fluid, having a foul, fecal odor. The omentum is adherent along the scar in the anterior abdominal wall and also to the parietal peritoneum in the left lower quadrant. The peritoneum is thickened and opaque, especially that part in the pelvis and both lower abdominal quadrants. At the splenic flexure is a firm mass measuring 12 by 8 cm. It is adherent to the parietal peritoneum, and behind it the colon seems to pass.

Intestine: Adjacent loops of intestine are lightly bound together by a fibrinopurulent exudate. Over the serous surface of the sigmoid and its mesentery and also the pelvic peritoneum are numerous nodules, varying in size from a few millimeters to 1 centimeter or more in diameter. These nodules are firm and often fused together. The nodules are most abundant along the mesenteric attachment of the sigmoid, and spread down over its serous surface, often as stiff plaques 2 cm. in length, and at a few places they almost encircle the intestine (Fig. 2). On section, they are silver gray in color and translucent.

The mucosa of the small intestine is negative. The lymphoid follicles and Peyer's patches are made out with difficulty. The ascending colon and the proximal half of the transverse colon are normal. In the distal half of the transverse colon are many ulcers in the mucosa, varying from 0.5 to 1.5 cm. or more in diameter. These are rounded or oval, with shelving edges and clean bases, and rarely extend deeper than the muscularis. One of the large ulcers on the inferior wall has perforated, the opening being more than 1 cm. in diameter. At the splenic flexure, the intestine is very sharply angulated and the lumen is much narrowed. The wall of the intestine in this region is tremendously thickened, very stiff and almost cartilaginous in consistence. In the wall of the intestine, usually in the serous portion, are many firm nodules about 0.5 cm. in diameter. The fat about the intestine contains similar nodules, and fibrous tissue is increased in it. (It was this infiltrated fat and thickened intestinal wall which was described as the mass at the splenic flexure, and also clinically as the spleen.) The mucosa of the descending colon and sigmoid contains many ulcers, similar to those described above. The rectum is negative except for a few nodules in the peritoneum over it.

Stomach and Duodenum: Stomach is negative, except for a stellate scar in the mucosa on the lesser curvature, and a few nodules similar to those described above in the serosa, also along the lesser curvature. The duodenum shows nothing unusual.

Lymph Glands: The mesenteric lymph glands are quite small and are found with difficulty. On section, nothing abnormal can be made out. The retroperitoneal glands are not enlarged; they are quite fibrous. The pelvic lymph glands are bound together by fibrous tissue. Some of them are fibrous, others contain firm, yellow, opaque material. They are not enlarged. Along the thoracic aorta are a few firm glands which on section contain considerable fibrous tissue. The mediastinal glands are only slightly enlarged. Those at the bifurcation of the trachea show an increase in fibrous tissue. Below the manubrium is a lymph gland which is slightly enlarged and soft. On section,

it is gray and translucent, with black pigment scattered through it. The cervical and axillary glands are quite small and on section show nothing unusual.

SPLEEN.—The spleen does not extend below the costal margin. It weighs 200 gm.; has a definitely nodular feel. On section there are seen in the pale grayish red pulp many moderately firm, opague, white, sharply circumscribed masses, measuring up to 1 cm. in diameter, and having a somewhat lobulated outline. The malpighian bodies are not easily seen. There is no apparent increase in fibrous tissue.

LIVER: The liver weighs 1,450 gm., and measures 22 by 21 by 9 cm. The capsule is smooth. Projecting above the surface are several white rounded

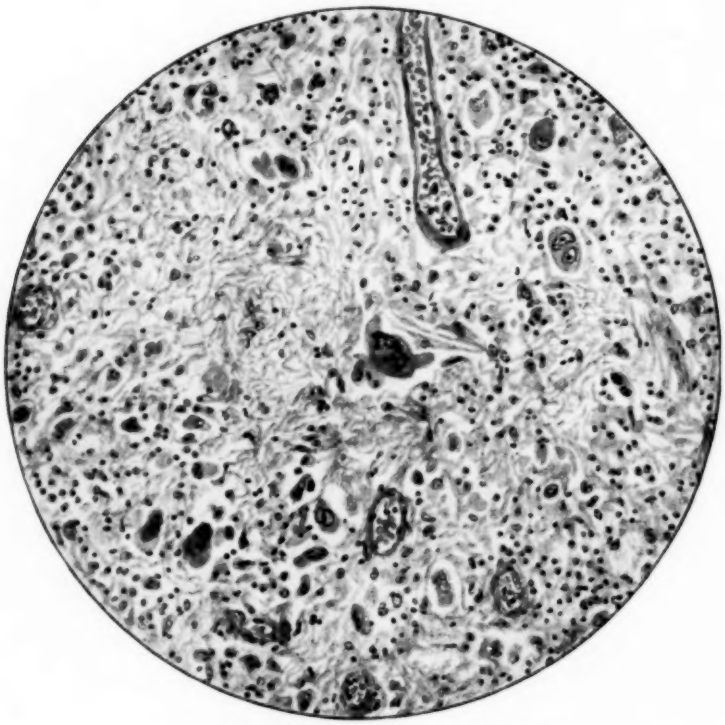

Fig. 3.—Hodgkin's disease. Gland from axilla.

nodules, the largest of which is in the postero-inferior part of the right lobe. On section, the pale reddish yellow surface is thickly studded with nodules varying in size from 1 mm. to one 3 cm. in its greatest diameter. The smaller nodules are gray and translucent; the larger ones are opaque and white. For the most part they are rounded, soft and sharply circumscribed. The large mass in the right lobe is soft, opaque and yellowish white, with a somewhat irregular outline. There is another large, similar mass close to the falciform ligament. The lobulation of the liver is uniform. There is no increase in connective tissue. The gallbladder is negative.

PANCREAS: The pancreas weighs 100 gm. The tail is densely adherent to the firm mass at the splenic flexure. This portion contains much fibrous tissue, running in wide strands through the parenchyma. Elsewhere, the pancreas is normal.

UTERUS: Normal.

OVARIES: The ovaries are quite small and fibrous, resembling in appearance the ovaries of an elderly woman. On section, a few corpora albicantia are seen. No follicles or corpora lutea are made out.

BLADDER: Negative, except for nodules in the peritoneum over it.

Aorta, kidneys, suprarenals and fallopian tubes are normal.

HEART: Weight, 210 gm. It is normal, except for a few firm, fibrous nodules on the mitral valve.

LUNGS: The left pleural cavity contains 400 c.c. of straw colored fluid. The right pleural cavity contains only a slight excess. Left lung: There are some dense adhesions between the apex of the lower lobe and the parietal pleura. The lung is crepitant, except for a firm area in the anterior part of the lower lobe. On section through this area, there is seen a small, firm, gray nodule surrounded by a zone of consolidation. Elsewhere the lung shows nothing unusual on section. In the parietal pleura at the site of the adhesions, there are many firm elevated nodules, resembling those seen in the peritoneum. These are grouped together and cover an area measuring about 6 by 4 cm. Right lung: Normal. The bronchial lymph glands are not enlarged and are quite black in color.

THYROID: Is slightly enlarged and firm. On section considerable colloid is seen.

Bacteriologic Report.—On culture, the peritoneal fluid contained *B. welchii*, enterococci, small gram-positive bacilli, *B. coli communis*, and *B. fecalis alkaligenes*.

Microscopic Examination.—LYMPH GLANDS: Axillary and cervical: The normal arrangement of the gland is lost; the germinal centers and sinuses are obliterated; the lymphocytes are reduced in number. Scattered throughout are many large cells, with one or more oval or indented vesicular nuclei, each containing a small amount of chromatin material and a single large nucleolus. Also, there are many multinucleated giant cells, having oval, rounded or lobed nuclei which appear to be solid. There is little increase in connective tissue. A few small necrotic areas are seen containing fibrin. The capsule is slightly thickened. There are no eosinophils. In the fat about the gland are small accumulations of plasma cells and lymphocytes (Fig. 3).

Retromanubrial: The lymphoid tissue has been almost entirely replaced by loose connective tissue, masses of giant cells with hyperchromatic nuclei, and endothelioid cells. In this new tissue are many small foci of necrosis, infiltrated with polymorphonuclear neutrophils. At one point, the capsule of the gland has been penetrated and the giant cells and connective tissue have extended into the surrounding fat. No eosinophils are seen.

Mesenteric: The germinal centers and sinuses are obliterated. The lymphoid tissue is rather loose. The capillaries in the gland are distended. There are many typical endothelioid cells. In some of these the nucleus has a vacuolated appearance, the nucleolus having disappeared. Only a few cells are present which have the hyperchromatic nuclei. A few areas of necrosis are found in which the cell outlines can still be discerned. The capsule has been invaded and in the surrounding fat are found giant cells, lymphoid and plasma cells and endothelioid cells. Occasionally, a single endothelioid cell is found lying free inside a fat cell.

Retroperitoneal: In one section, fibrous tissue is tremendously increased and passes in dense and wide bands throughout the gland, and also is scattered diffusely through it. Between the larger bands of fibrous tissue are small pockets of lymphoid cells, among which are found typical endothelioid cells

and a few of the giant cells with densely staining nuclei. In another section, the fibrosis is even more marked; there are fewer endothelioid cells. A moderate number of polymorphonuclear neutrophils are found.

Pelvic: The greater portion of the gland consists of caseous material, in which are found nuclear fragments and cholesterin crystal clefts. About the periphery of this necrotic area are a few epithelioid cells and mononuclear phagocytes containing brown pigment. There are also irregular masses staining blue, lying in clear spaces having the outlines of cells. With silver nitrate and purpurin preparations these are found to be masses of calcium, and are most probably calcified nuclei.

In sections of glands stained with the Wilson stain, the nucleoli of the typical endothelioid cells stain with varying intensity with eosin. Often in the other giant cells, a large nucleolus stands out brilliantly stained with eosin in the center of the solid blue staining nucleus. The cytoplasm of these latter cells likewise takes a more intense stain with eosin than does that of the endothelioid cells (Fig. 4).

Spleen: The sinuses are rather wide, and connective tissue is increased. Accumulations of endothelioid cells and polymorphonuclear leukocytes, together

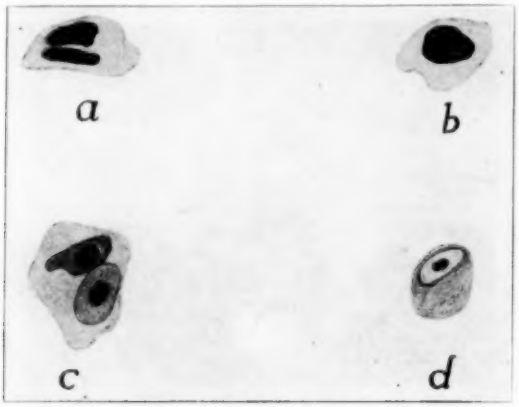

Fig. 4.—Hodgkin's disease. a and b, atypical giant cells; hematoxylin and eosin stain. c, atypical giant cell; Wilson stain. d, endothelioid cell.

with eosinophils often occupy the site of the malpighian bodies. In some of these, there is necrosis of the central part. Several of the vessels are surrounded by masses of the Hodgkin's granulation tissue.

Pancreas: The interlobular septa are widened by an increase in dense connective tissue in which are accumulations of small wandering cells and occasionally a few of the giant cells with hyperchromatic nuclei and typical endothelioid cells. The parenchyma and islands are normal.

Liver: In many of the lobules the cells about the portal areas are filled with fat. There are masses of loose connective tissue in which are many large cells with multiple hyperchromatic nuclei. A few eosinophils are found in these groups. In the larger of these there is often central necrosis. At the margins of some of the nodules, the giant cells are found out in the sinusoids, and the liver cells about them are indented or flattened out. Occasionally giant cells are also found in sinusoids at a distance from the nodules.

Kidney: Normal.

Suprarenal: Normal.

SMALL INTESTINE: Normal, except for a fibrinopurulent exudate on the serous surface.

COLON: In the lymphoid follicles are seen many of the giant cells with densely staining nuclei. In the submucosa are large masses of loose connective tissue and small round cells, with intermingled giant cells. In some of the larger masses, the central portion has undergone necrosis. In the serosa and surrounding fat are seen large accumulations of the giant cells with hyperchromatic nuclei, and virtually none of the characteristic endothelioid cells. The giant cells are found extending up between the muscle bundles of the longitudinal muscle, although generally the muscle is lifted up by the new growth of tissue. The new tissue also extends to the blood vessels, but does not invade the vessel wall. A few eosinophils are found.

OVARY: The blood vessels stand out prominently. Several corpora albicantia are present which have a much less compact appearance than usual. Also there are several areas which appear to be recent corpora albicantia, but which contain great numbers of cells loaded with coarse brown granules. No follicles are to be differentiated.

HEART: The myocardium is normal.

LUNG: Just beneath the pleura are several groups of alveoli having thickened walls. Some of the alveolar spaces are filled with a granular material and a few small mononuclear cells. Others are full of small wandering cells, and among these are typical endothelioid cells and a few of the giant cells with dense nuclei.

PARIETAL PLEURA: This is greatly thickened and edematous. There is a diffuse infiltration with small round cells, polymorphonuclear neutrophils, and large mononuclear cells. Dense accumulations of small round cells, many having hyperchromatic nuclei, are scattered through the section, but especially just beneath the pleural surface.

Treatment.—Aside from sedatives, the only therapeutic measures used were transfusions and the roentgen-ray.

TRANSFUSIONS: Nine transfusions were given. At first they were given because of the severe anemia and weakness. Immediately after transfusion there was a rise of temperature and a chill six out of nine times. In a few hours, however, the temperature would fall and the patient would be much improved for from a few days to a month. It is impossible to say how much of this improvement was due to the treatment, but undoubtedly the transfusions had a definite, if limited, beneficial effect.

Some of the drops in the temperature were very striking, and the improvement in the general condition of the patient was just as marked. On only two occasions did the temperature remain elevated after transfusion. One of these occasions occurred just before death.

ROENTGENOTHERAPY? The patient was treated ninety-five times, but in many cases more than one area was irradiated. This treatment was begun under the guidance of Dr. Corscaden. The Coolidge tube and Solace apparatus were used. The filters were changed several times. They were: first, 3 mm. aluminum, 1 cm. wood; second, 1 mm. aluminum, 1 cm. wood, 3 mm. glass, 4 mm. leather; third, 1 mm. aluminum, 1 cm. wood, 3 mm. glass, 4 mm. leather, 2 mm. bakalite; fourth, 1 mm. aluminum, 1 cm. wood, not used, 4 mm. leather, 2 mm. bakalite. The voltage was 80 or 90 kilovolts. The current was 5 milliamperes. Anodal distance from skin, 25 cm. Dosage at first was 45 milliampere minutes; this was increased to 50, and at the last reduced to 35 milliamperes.

The whole of the body, anterior and posterior, was divided into areas. The numbers of these areas were changed from time to time, but were always so arranged that all the contents of the thorax and abdominal cavity were exposed to the rays.

Originally the plan was to have the patient treated twice a week, choosing the areas so that the whole of the trunk would be irradiated once in three

weeks. Owing to the fact that the patient was not always in the hospital, it was frequently found impossible to adhere to this plan.

Frequently the treatments were followed by nausea and vomiting; this reaction would last for a few hours.

Because of the low white blood cell count (between 3,000 and 4,000) and general weakness, the patient was given no roentgenotherapy for six months prior to death.

DISCUSSION

Roentgenotherapy was first used in the treatment of Hodgkin's disease about 1900. Among the first to report cases were Pusey,[6] and Williams [7] in 1902. The following year Childs,[8] and Finch [9] contributed to the literature. Three years later Pfieffer [10] wrote an article. These early papers are interesting but frequently lacking in details. Indeed, in some instances they are only brief letters expressing the writer's views in regard to his results.

Among the more recent writers are Hocguertel,[11] Krecke,[12] Sanguinetti,[13] Holding,[14] Levin [15] and Knox.[16] It is unfortunate that none of these observers report the effect of the roentgen ray on the glands. In a paper just published Mueller [17] describes two cases, detailing the microscopic appearance of the glands after treatment.

Our patient was treated ninety-five times with roentgen rays. It is impossible to say just what effect this had on the course of the disease; apparently, the glands decreased in size, especially the cervical nodes. As is frequently the case, the patient was usually nauseated and occasionally vomited after the treatment. This discomfort generally lasted for several hours. After the immediate effect of the treatment wore off, the patient would often seem to feel better and it was believed that the rays had a beneficial effect.

Course.—The progress of the disease may be described as being slowly progressive; there were periods when she would be very ill. These periods would be followed by intervals when she would feel much better. As time went on, the acute stages became longer and the improvement less marked. The loss of weight was constant. The transfusions evidently helped her, but the effect was not lasting.

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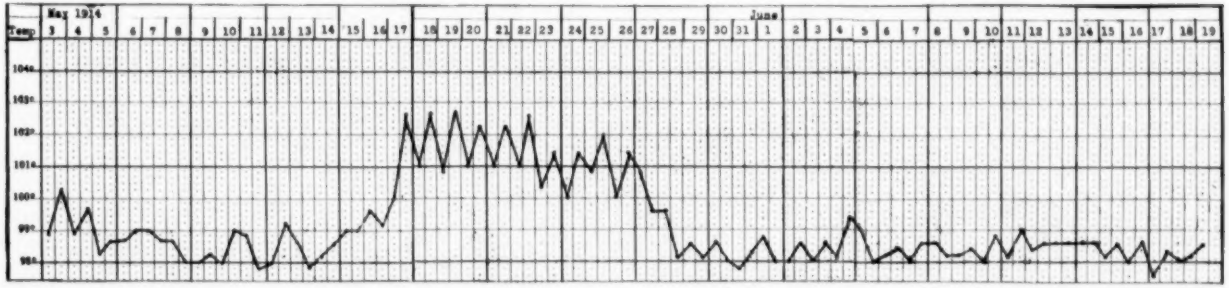

Chart 1

The temperature charts are given at such length, because it is very interesting to see the constant remissions, as well as falls in temperature occasioned by transfusions. Charts 1 and 2 were made at the time of the first admission and antedated the others by more than five years. Beginning with Chart 3, the whole of the record of the last admission is shown. Radio = radiotherapy. Trans. = transfusion. Aspir. = aspiration.

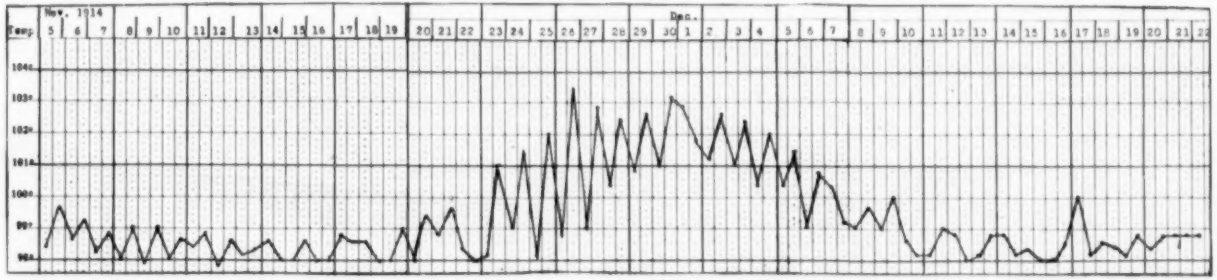

Chart 2

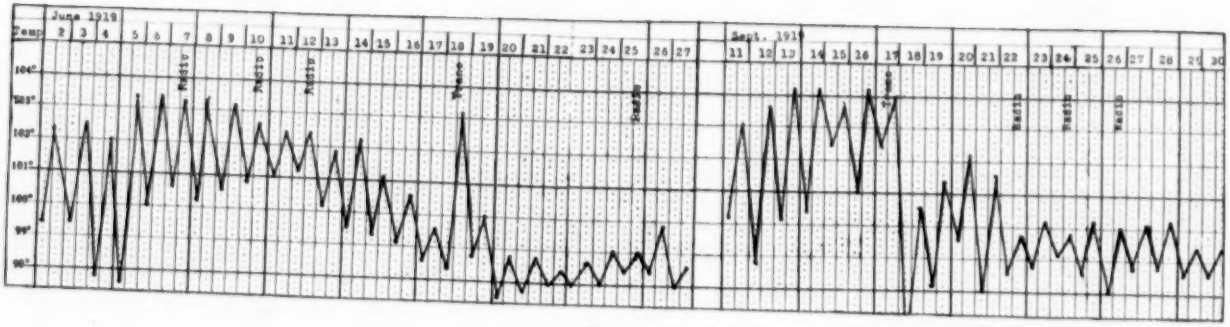

Chart 3

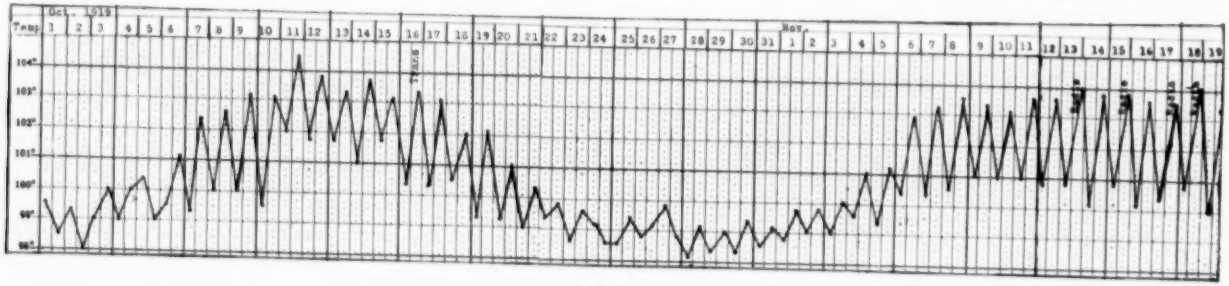

Chart 4

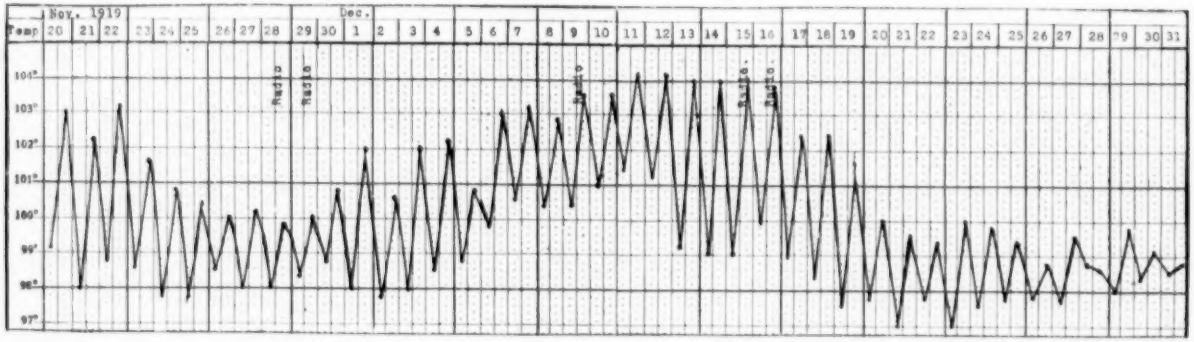

Chart 5

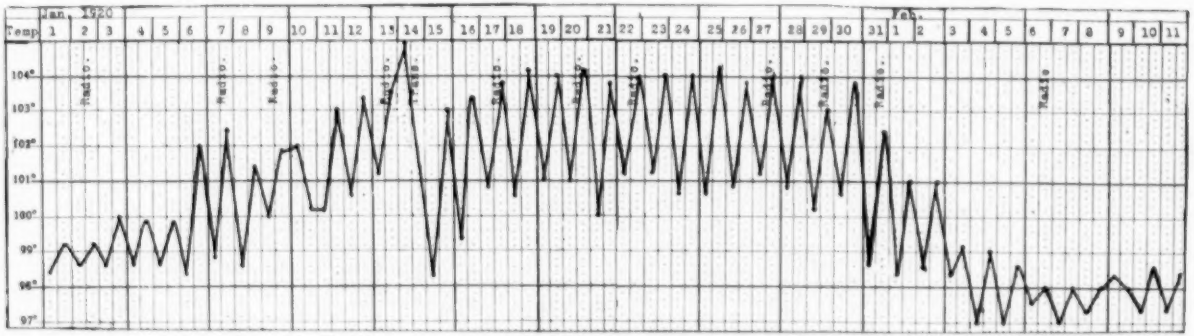

Chart 6

Fever.—When first seen, she ran an intermittent temperature similar to that described by Ebstein,[18] Murchison,[19] Pel,[20] Ziegler[21] and Musser[2] (Charts 1 and 2). Then for varying intervals, there would be no fever, and after a while the recurrent type would reappear. During the last admission the recurrent type was the rule (Charts 3 to 11). The temperature was, apparently, affected by the roentgen ray and the transfusions, but it is doubtful if either of these measures had any real effect on the course of the fever. Although she had been having a high fever for almost a month just before she died, on other occasions she had just as high a temperature and it lasted for a similar period (Chart 6).

Blood Counts.—The blood examination is interesting because the picture resembled that described by Bunting[22] in Hodgkin's disease. There usually was an increase in the white blood cells during the first admission, the total count was as high as 12,000. The large mononuclear

TABLE 1.—EFFECTS OF TRANSFUSIONS

Transfusion	C.c.	Red Blood Cells		Hemoglobin, per Cent.	
		Before	After	Before	After
First	450	3,800,000	4,500,000	65	70
Second	400	3,100,000	3,700,000	50	65
Third	350	2,700,000	3,600,000	50	55
Fourth	300	2,600,000	3,200,000	40	40
Fifth	300	3,000,000	4,000,000	40	60
Sixth	300	3,500,000	3,100,000	60	60*
Seventh	300	1,800,000	2,200,000	40	80
Eighth	300	4,500,000	Not done	75	
Ninth	250	1,700,000	.....	35†	

* Not taken immediately after transfusion.
† The patient died the next day.

cells and transitionals were increased. The platelets were always increased, running as high as 570,000, even after many treatments with the roentgen rays.

Later the white cells were reduced as low as 2,200. This was thought to be due to the effect of the irradiation and on this account the treatment was stopped.

The anemia was progressive and very marked toward the end of the illness. During the first year, the red cells numbered as high as 4,800,000, with 81 per cent. hemoglobin. The anemia increased until a few days before death, when the red cells numbered 1,700,000, and the hemoglobin was 35 per cent.

The effects of the transfusions are shown in Table 1.

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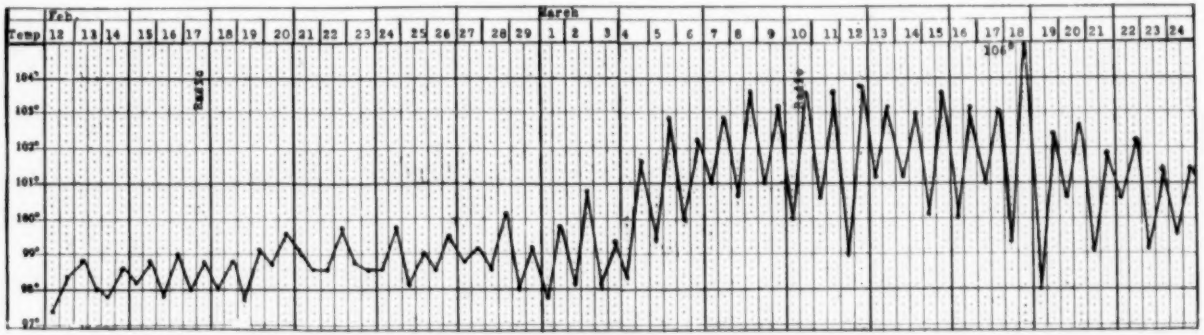

Chart 7

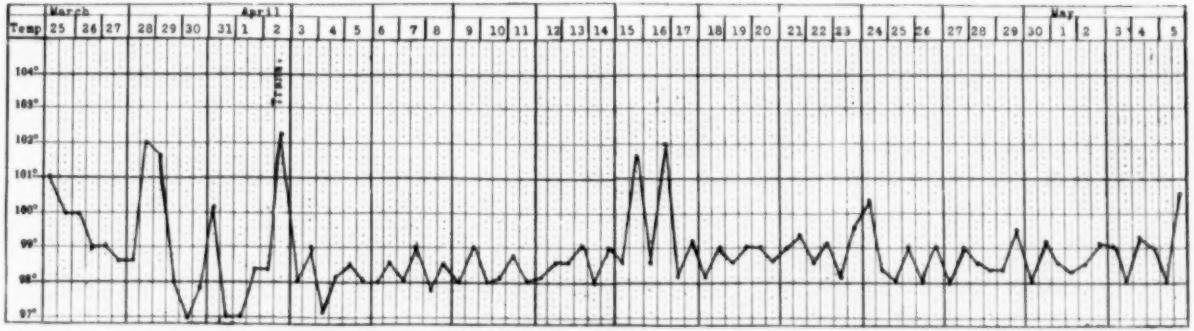

Chart 8

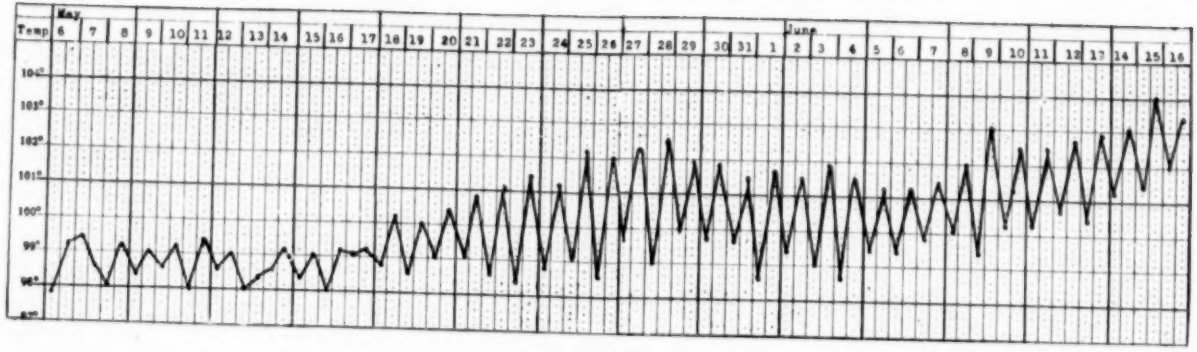

Chart 9

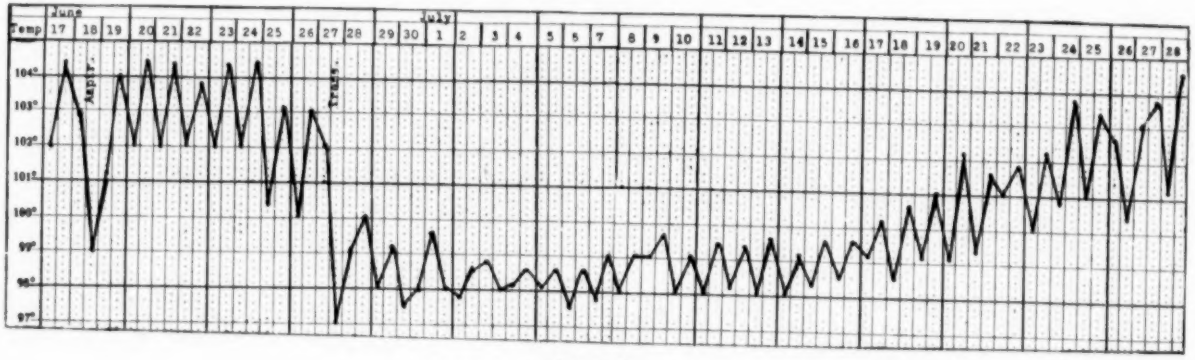

Chart 10

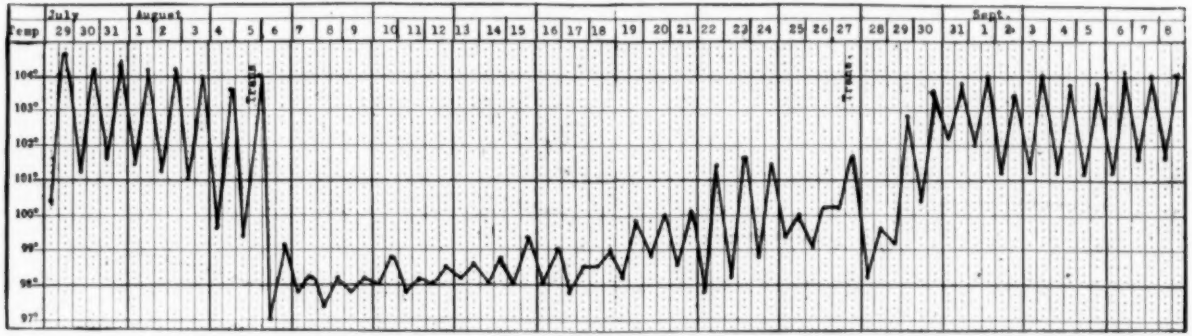

Chart 11

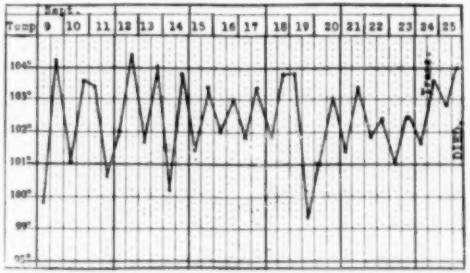

Chart 12

It is unfortunate that the data are not more complete. However, they show that the transfusions had a beneficial, if temporary, effect on the red cells and the hemoglobin. It is very difficult to account for the change between the seventh and eighth transfusions. The increase of more than 2,000,000 cells, and of 25 per cent. in the hemoglobin

TABLE 2.—Blood Counts

Date	Transfusion, C.c.	Red Blood Cells	Hemoglobin, per Cent.	White Blood Cells	Polymorphonuclears, per Cent.	Basophils, per Cent.	Eosinophils, per Cent.	Small Lymphocytes, per Cent.	Large Lymphocytes, per Cent.	Large Mononuclears per Cent.	Transitionals, per Cent.	Platelets
1914												
3/ 7	...	4,000,000	60	10,000	75	...	1	24				
7/ 7	...	4,000,000	74	12,800	74							
11/28	...	4,880,000	81	10,000	75	...	...	25				
1915												
3/ 1	...	4,540,000	..	8,140	71	0.5	5.5	14	..	...	9	
11/14	...	4,430,000	85	9,500	75.5	1.5	0.5	14.5	..	4.5		
1919												
1/15	...	4,470,000	50	5,000	72	...	...	2.0	23	3		
6/ 4	...	3,800,000	65	3,800	72	...	1	3.0	..	21	3	
6/18	450											
6/20	...	4,450,000	70	4,300	74	...	2.0	13.0	10	1	...	496,000
6/24	...	4,400,000	80	4,200	74	...	2.0	8.0	..	9	7	
7/23	...	3,900,000	73	5,700								
9/10	...	.....	..	6,800	67	...	...	10	20	...	3	
9/16	...	3,100,000	50	5,600								
9/17	400											
9/19	...	3,700,000	65	9,200	80.5	...	0.5	18.5	..	0.5		
9/22	...	3,300,000	60	5,200	77	...	0.5	20.5	..	0.5	1.5	
9/30	...	4,300,000	65	6,800	83	...	...	....	..	...	2	
10/15	...	2,700,000	50	6,400	85	...	...	10	4	...	1	
10/16	350											
10/20	...	3,640,000	55									
11/12	...	3,870,000	60									
12/11	...	3,840,000	60-70	10,000	79.6	0.2	0.2	3.0	..	34	13.6	340,000
1920												
1/12	...	2,600,000	40	4,700								
1/14	300											
1/17	...	3,240,000	40									
2/ 4	...	3,200,000										
2/11	...	.....	..	3,700	77	0.4	1.2	8.8	..	2.4	9.4	320,000
3/13	...	3,200,000	50									
3/16	...	.....	..	2,200								
4/ 2	...	3,600,000	40									
4/ 2	300											
4/ 8	...	4,640,000	60	3,600	55	...	1	44	..	1		
5/11	...	3,500,000	60-70	6,000	55	1	1	42				
5/12	...	.....	..	9,200	78.4	0.8	3	13	..	0	4.8	570,000
6/18	...	.....	..	6,000	71.2	0	0.2	14.2	..	1.2	5.6	520,000*
6/27	300											
7/22	...	3,100,000	60	5,700	71	...	...	8	21			
8/ 5	...	1,800,000	40	6,000								
8/ 5	300											
8/ 6	...	2,300,000	50	3,200								
8/10	...	3,000,000	60	4,200								
8/27	...	4,500,000	75	7,900	72	...	...	28				
8/27	300											
9/23	...	1,750,000	35	5,600								
9/24	250											

* Unclassified, 7.6.

seems rather improbable, especially as the patient did not seem to be any better. It is impossible to exclude the possibility of a technical error.

Symptoms and Physical Signs.—The blood pressure was always low, even in the early part of the disease when the patient was up

and about. This has been observed in Hodgkin's disease before (Longcope and McAlpin[23]), and is of interest but probably not of any great importance.

Hydrothorax: It was necessary to aspirate the chest four times during the last admission. This condition is frequently found in Hodgkin's disease, and has been mentioned by Ziegler,[21] Edsall,[24] Lemon and Doyle,[25] and by Longcope and McAlpin.[26] It is probably due to involvement of the pleura. The chest was aspirated three weeks before death, and at the postmortem examination the left pleural cavity contained 400 c.c. of straw colored fluid.

Abdominal Symptoms.—For several months before death, the patient complained of pain in her right side, and in this region a large mass was readily palpated. It was supposed to be the spleen, and the pain was attributed to a perisplenitis. The necropsy showed the spleen to be only slightly enlarged (weight 200 gm.), but there was a large mass made up of infiltrated fat and intestinal wall that had been mistaken for the spleen.

About fifteen months before death, the patient began to complain of abdominal pain. During these attacks the abdomen would become distended. Relief was obtained by various therapeutic measures, such as lavage, cathartics (in the early stages) and edemas. At first these attacks were of short duration and not very serious, but during the last few weeks they became a great problem. Finally, it was deemed advisable to operate, although the patient was an extremely poor surgical risk. Before this was done, an enema was given in the "knee chest" position, with satisfactory result. The relief was only temporary and in a few days the symptoms returned. The patient was in great distress, requiring sedatives. She became very weak, did not react to stimulants and died.

RÉSUMÉ

1. The diagnosis of Hodgkin's disease of the mesenteric lymph nodes was made six and one half years before death. The patient was under observation from the time the diagnosis was made until she died.

2. The temperature at times was of the recurrent type, described by Ebstein,[18] Murchison,[19] Pel[20] and Ziegler.[21]

3. The blood picture closely resembled that described by Bunting.[22]

4. The blood pressure was very low, even when the patient was first admitted (Longcope and McAlpin[23]).

23. Longcope, W. T., and McAlpin, K. R.: Oxford Med. **4**:20.
24. Edsall, D. L.: New York M. J. **82**:838, 1905.
25. Lemon, W. S., and Doyle: Am. J. M. Sc. **172**:516, 1921.
26. Longcope, W. T., and McAlpin, K. R.: Oxford Med. **4**:17.

5. Although the spleen was thought to be very much enlarged during life, at necropsy it was found to be only a trifle larger than normal. Apparently a mass of infiltrated fat and intestinal wall had been mistaken for the spleen.

6. The hydrothorax that required paracentesis is not unusual in this disease, and is probably due to involvement of the pleura. Cases have been described by Lemon and Doyle,[25] Ziegler,[21] Longcope and McAlpin.[26]

7. Because of the advanced stage of the disease when the diagnosis was made, it is safe to say that the roentgenotherapy slowed the process but in no sense cured the condition.

8. Death was due to perforation of the intestine. This is believed to be very unusual in Hodgkin's disease.

9. Unusual pathologic findings are: Extensive involvement of the peritoneum and abdominal viscera; the tendency to regional invasiveness; atypical giant cells and the scarcity of eosinophils.

We are deeply indebted to Dr. Warfield T. Longcope and Dr. A. M. Pappenheimer for suggestions and advice.

EXPERIMENTAL REPRODUCTION OF THE SPECIFIC HISTOPATHOLOGY OF INFLUENZA *

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NEW YORK

It was realized rather early in the recent pandemic of influenza that by the time patients died secondary infections with various pyogenic organisms had usually taken place, which more or less completely obliterated evidences of the original disease. From numerous bacteriologic studies, it was evident that the bacteria recovered from the lungs after death had secondarily invaded the damaged organs from the upper respiratory tract. Traditional belief made many observers reluctant to assign a similar rôle to the *B. influenzae* of Pfeiffer. But even this organism was finally relegated to a secondary rôle by work such as that of MacCallum,[1] which demonstrated that although it might be present in a large percentage of the lungs of persons dying of the disease in one part of the country, the bacillus of Pfeiffer was correspondingly rare in the lungs in other parts of the country where, at the time, it happened to be a less frequent resident of the upper respiratory tract.

Such advances in our knowledge of the bacteriology of the disease immediately concentrated the efforts of pathologists on an attempt to differentiate the secondary purulent from the primary fundamental lesions of epidemic influenza. The best work in this country (Klotz;[2] Winternitz, Wason and MacNamara[3]) kept this aim constantly in view, as did the best of the European observers (Oberndorfer,[4] Dietrich,[5] Glaus and Fritzche,[6] Marchand,[7] Soerensen,[8] Koopman[9]). Some of these authors (Klotz, Oberndorfer, Glaus and Fritzsche, Koopman) had the unusual opportunity to study fulminating cases of the disease in persons who had died within forty-eight hours after the onset, before the secondary infection had sufficiently invaded the damaged lung to obscure the primary pathological picture.

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* From the Pathological Department of the Mount Sinai Hospital.
* Work done during the tenure of a George Blumenthal, Jr. fellowship in pathology.

1. MacCallum: J. A. M. A. **72**:720 (March 8) 1919.
2. Klotz: Studies on Epidemic Influenza, Published from University of Pittsburgh School of Medicine, 1919, p. 207.
3. Winternitz, Wason and MacNamara: The Pathology of Influenza, Yale University Press, 1920.
4. Oberndorfer: München. med. Wchnschr. **65**:30, 1918.
5. Dietrich: München. med. Wchnschr. **65**:34, 1918.
6. Glaus and Fritzsche: Cor.-Bl. f. schweiz. Aerzte **48**:1121, 1918; ibid. **49**:72, 1919.
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8. Soerensen: Ztschr. f. Hygiene u. Infectionskr. **91**:204, 1921.
9. Koopman: Virchows Arch. f. path. Anat. **228**:319, 1920.

Specificity of the Histopathology of Early Human Influenza.—Summarizing the work of these authors, one is impressed with the unanimity of their opinion that the pathologic process in early human influenza represents a specific tissue reaction, not to be seen in the lungs in any other type of infection. In fact, Winternitz and his collaborators state in their monograph: "The histology of this disease is almost as specific as that of any biologic reaction."

The essential features of the pathologic lesions in early human influenza are (1) congestion, edema and often minute hemorrhages in the mucous membrane of the trachea and larger bronchi; (2) patchy distribution of the pulmonary lesions; (3) diffuseness of the process, which often extends through several lobes or even parts of all lobes; (4) profuse serosanguinous exudate which drips from the moist cut surface of involved parenchyma; (5) hemorrhagic character of the lesion, the hemorrhagic exudate being seen microscopically to infiltrate the interstitial tissue and fill patches of alveoli; (6) aplastic character of the process, the inflammatory exudate in alveoli and interalveolar interstitial tissue being composed almost entirely of red cells and serum with an occasional endothelial cell but containing astonishingly few polymorphonuclear or other leukocytes. In addition, Klotz directed special attention to the tendency to emphysematous overdistension of alveolar air spaces in the involved lungs; and Winternitz also emphasized the tendency to necrosis of the epithelium lining the trachea and bronchi and to hyalin necrosis of pulmonary tissue, especially of interalveolar septa in the damaged areas. One of us had considerable experience with the study of this unusual type of pulmonary inflammatory process, while serving during the pandemic as director of laboratories for the group of U. S. Army Base Hospitals at Beau Désért Hospital Center, France.

Experimental Reproduction of Influenza.—Just as advances in bacteriology during the first year of the pandemic (1918) were in large part responsible for a more accurate conception of the pathologic phenomena involved in influenza, so, in similar manner, the more recent bacteriologic investigations of Olitsky and Gates [10] and of Loewe and Zeman [11] have afforded renewed opportunities for a study of the essential features of this pathologic process. Independently of one another and simultaneously, these two groups of investigators succeeded in cultivating a filtrable virus from the nasopharyngeal washings made early in the course of the influenza, which is capable of producing lesions in the lungs of rabbits, grossly and microscopically identical with those found in human beings suffering from the disease.

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10. Olitsky and Gates: J. Exper. M. **33**:125, 1921.
11. Loewe and Zeman: J. A. M. A., **76**:986 (April 9) 1921.

We have, therefore, undertaken to study more minutely the pathologic process induced experimental in these animals by the intra tracheal inoculation of cultures of these punctiform, filtrable bodies and of influenza virus (filtered human nasopharygeal washings or lungs from inoculated animals). In this manner we have been able to observe the lesions at the very earliest stages of their development, an

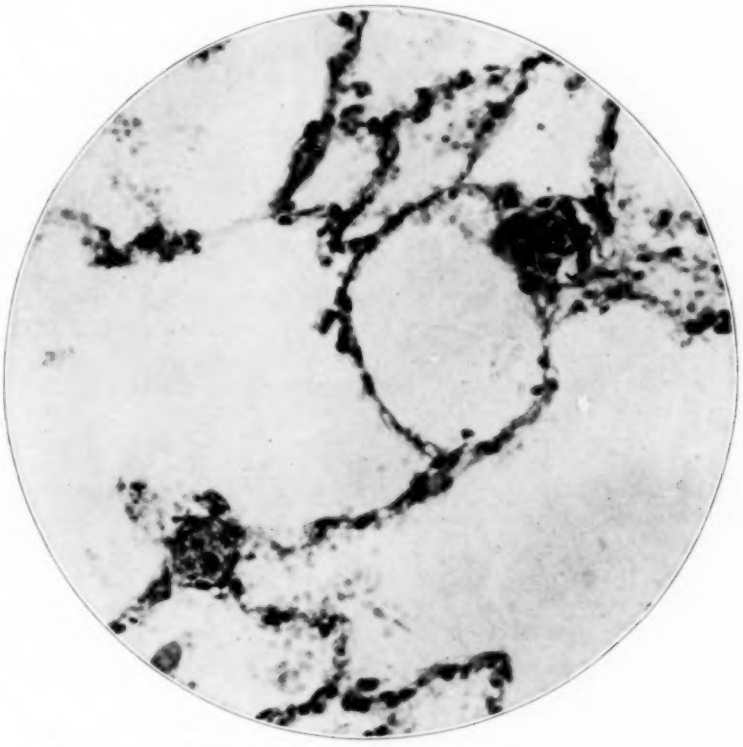

Fig. 1.—Section from portion of lung showing minimal amount of parenchymal damage. Shows (1) emphysematous overdistension of alveoli, (2) congestion, (3) beginning extravasation of red blood cells into the alveoli, (4) two capillaries cut in cross section which are widely dilated and are occluded by blood platelet thrombi. (×400.)

opportunity obviously impossible in human beings. And this opportunity has enabled us, we believe, to throw more light upon the pathogenesis of the disease.

Materials employed.—Four series of rabbits were inoculated intratracheally with the following materials:

(1) Human nasopharyngeal washings: In the first series, animals were inoculated with nasopharyngeal washings from early cases of

influenza. These washings were obtained in the manner described elsewhere,[11] within twenty-four hours after the onset of the first symptoms of illness, and they were then carefully filtered under strict sterile precautions through Berkefeld filters size N or Mandler filters of corresponding density. The filters were always tested with *B. prodigiosus*. The filtered nasopharyngeal washings were then cultured aerobically and anaerobically in ordinary laboratory mediums and found to be free of contaminations. Inoculations were also made on the so-called chocolate agar medium in order to eliminate the possible presence of *B. inflenzae* of Pfeiffer or other hemoglobinophilic organisms. From 1 to 3 c.c. of the clear filtrate were used for the intratracheal inoculations, the material being introduced in the manner subsequently to be described.

(2) Filtrates of glycerolated lungs of inoculated animals: In a second series, the injected material consisted of the lungs of animals in series one and three, which had been glycerolated for a variable period (from one week to fourteen months) and then filtered through Berkefeld or Mandler filters. The lungs were removed in sterile fashion from the animals within from thirty-six to forty-eight hours after inoculation and were not further utilized unless found to be free of all secondary invading organisms. Glycerolation was often employed as an added precaution as it did not seem to affect the virulence of the material appreciably.

(3) Cultures of the punctiform bodies. In the third series, the rabbits were inoculated intratracheally with cultures of the minute punctiform filtrable bodies isolated by Loewe and Zeman. Most of the cultures were obtained from the filtered nasopharyngeal washings of early cases of influenza, persons in the first twenty-four or thirty-six hours of their illness. Other cultures were derived from the lungs of animals which had originally been inoculated intratracheally with the filtered nasopharyngeal washings of early human cases of influenza. And a third group of cultures employed was recovered from the lungs of animals in which the experimental disease had been produced by the inoculation of cultures isolated from such nasopharyngeal washings.

One interesting feature of this third series of experiments is that the cultures of this filtrable virus, after being kept at incubator temperature for fourteen months, were not only found to be still viable, but also retained their unique pathogenic properties. Similarly, the lungs of animals in which the disease had been produced by intratracheal inoculation of human nasopharyngeal washings could be preserved in 50 per cent. glycerol, and after fourteen months the glycerolated material was viable and also retained an almost undiminished infectivity.

(4) Control experiments: The fourth series of experiments served as controls to series one, two and three. The inoculated materials in this series consisted of the following:

(a) Culture medium: ascitic fluid containing kidney tissue and layered with petrolatum, which had not been inoculated but had been incubated at 37 C. simultaneously with the inoculated cultures for varying periods of time up to fourteen months.

(b) Berkefeld filtrates of glycerolated lungs of rabbits succumbing to intercurrent laboratory infections or to the intratracheal inoculation of various pyogenic organisms.

(c) Filtrates of nasopharyngeal washings obtained in the customary manner from patients suffering with diseases other than influenza. Surgical cases were preferred to rule out possible contact infection.

(d) Cultures of *Staphylococcus aureus, Streptococcus hemolyticus, Streptococcus anhemolyticus,* pneumococcus and *Bacillus bipolaris* (distemper).

(e) Cultures of *B. influenzae* of Pfeiffer which were derived from various sources such as (1) nasopharynx of normal individuals; (2) cerebrospinal fluid of influenzal meningitis; (3) nasopharynx, sputum and lungs of persons suffering from influenza during the pandemic.[12]

Technic of Inoculation.—The rabbit, having been lightly anesthetized with ethyl chlorid,[13] from 1 to 3 cc. of culture or other material was inoculated intratracheally. In a few experiments this was accomplished by passing a fine rubber catheter into the trachea in the manner of the Meltzer-Auer method of intratracheal insufflation. It was found to be more satisfactory to inject the material directly through the tracheal wall by means of a fine needle and syringe, after previous removal of the hair with barium sulphide and sterilization of the skin with tincture of iodin.[14] The animals immediately recovered from the very transient anesthesia and presented no evidence of any distress.

Symptoms of Illness.—Often the first evidences of illness made their appearance within a few hours after the inoculation. Within twenty-four hours, the animals appeared to be severely ill, their movements were less active, breathing was more rapid, and the conjunctivae were injected. Over both sides of the chest, the stethoscope elicited numerous moist räles and, in some animals a distinct expiratory, asthma-like wheeze.

Leukopenia.—Simultaneous with the development of these symptoms, there appeared a pronounced leukopenia, the number of leukocytes in the blood at times decreasing from 50 to 60 per cent. within

12. For many of the strains we are indebted to Dr. William H. Park of the Research Laboratory of the New York City Board of Health.

13. Ethyl chlorid was employed owing to the ease and rapidity with which a light anesthesia could be induced. It was proven that this volatile drug as used was incapable of producing any structural changes.

14. Direct intratracheal inoculation was performed with 18-gage needles connected to 5 c.c. Luer syringes. Entrance into the trachea was indicated by the easy withdrawal of air upon elevating the plunger of the syringe.

forty-eight hours. The leukopenia was present in every instance after the inoculation of either active influenza virus (filtered lungs or nasopharyngeal washings), or cultures obtained from the virus. It was never encountered in animals inoculated with pyogenic organisms or with *B. influenzae* of Pfeiffer; on the contrary, even the latter regularly induced a definite hyperleukocytosis.

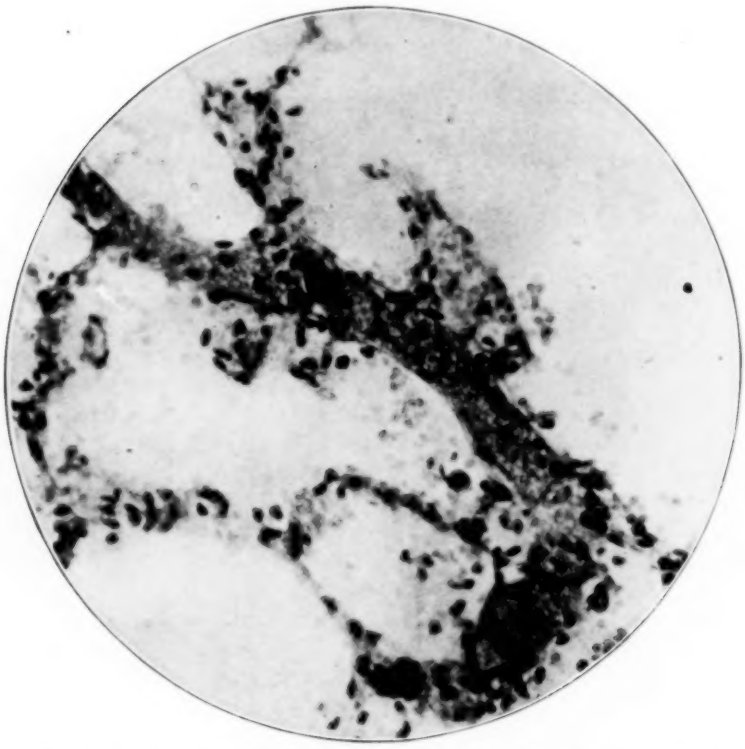

Fig. 2.—Section showing an occluded arteriole and its tributary capillaries cut longitudinally. The outlines of the blood platelets comprising the thrombus can be made out, even with this magnification. Although the thrombus contains a few polymorphonuclear and mononuclear leukocytes, the cellular forms of inflammatory exudate are conspicuously absent in the alveolar air spaces and interalveolar tissue. In this microscopic field the alveolar spaces contain serum and red blood cells, whereas in other portions of the same section the interstitial tissue is the more extensively infiltrated with the aplastic serosanguineous exudate. (×400.)

Secondary Invasion with Pyogenic Organisms.—At the very beginning of the work, it was immediately observed that animals which were permitted to live longer than from forty-eight to seventy-two hours

after the onset of the disease usually developed various types of secondary infection within their damaged lung parenchyma. Exactly as in human influenza, the primary process then became obscured by complicating lesions such as pneumonic consolidations, abscesses, empyema, etc., from which various pyogenic organisms could be isolated. Simultaneous with the onset of this secondary bacterial invasion, the leukopenia rapidly gave way to a hyperleukocytosis.

It was therefore necessary to confine the study to the lungs of rabbits which were sacrificed [15] within from twenty-four to forty-eight hours after the inoculation. The following observations therefore represent the earliest lesions of the experimental disease, at a time when cultures from the damaged lung were negative—except the filtrable organisms described by Olitsky and Gates and by Loewe and Zeman.

Gross Pathology.—The lungs are usually voluminous and present a striking picture of acute emphysema. Although the process is often bilateral, usually one lung or parts of a lung are more extensively involved. The normal pale yellowish gray surface of the organ is mottled with deep pink in large diffuse areas. Here and there in these pink areas are small hemorrhagic foci, usually diffuse in outline.

A frothy edema fluid is often present in large quantity in the lumen of the trachea and larger bronchi. The mucous membrane of the latter regularly shows intense congestion and edematous swelling and is often stippled with minute hemorrhagic points.

On section of the lungs, no areas of firm consolidation are discoverable. The large pink areas appear to be chiefly the site of an intense congestion and edema, so that the cut surface drips a blood stained fluid. Within the confines of the pinkish lung tissue there are areas of swollen lung parenchyma of a deeper red which present the appearance of red jelly, but are compressible and moist. Often the affected portion of a lobe is a deep pink at the periphery, shading to a darker red at the hilus. In these red areas, some small dark hemorrhages, pinpoint to pinhead in size, are frequently discernable. Between the areas of involved parenchyma, the lung presents merely an intense emphysema.

Microscopic Picture.—On microscopic examination, the salient feature of the pathologic process are: (1) congestion and edema and occasional small hemorrhages in the tracheal mucosa; (2) small hemorrhages into the walls of bronchi and the presence of red blood cells in the bronchial lumen; (3) emphysematous overdistension of alveolar air spaces; (4) congestion, and in many places, edema of areas of lung parenchyma both interstitial and interalveolar; (5) hemorrhagic extra-

15. The animals were killed by a single sharp blow over the suboccipital region. Death was instantaneous.

vasations into the interstitial tissue of the alveolar walls with a great tendency for the hemorrhage to break into the alveolar air spaces, filling smaller or larger groups of them with red blood cells; (6) absence of ordinary cellular inflammatory exudate; (7) occlusion of numerous interalveolar and interstitial capillaries and arterioles by blood platelet thrombi. Except for the vascular lesions, all the other phenomena were also observed by Olitsky and Gates in their experimental animals.

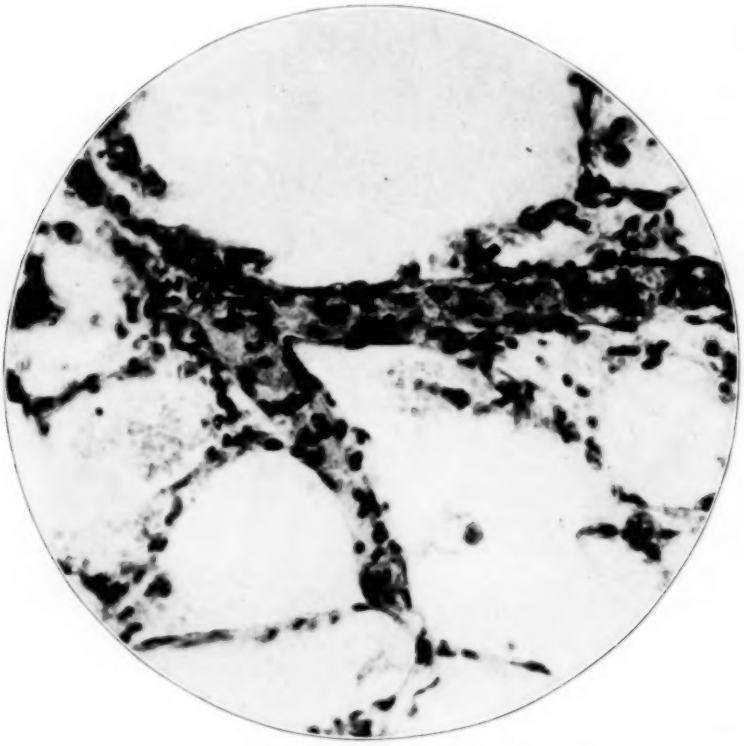

Fig. 3.—Section showing dilated and branching capillary occluded by blood platelet thrombus. The endothelial cells of the capillary wall are swollen and at several sites can be seen to have undergone proliferation. (× 400.)

The changes in the tracheal and bronchial mucosa occur with great regularity. Similarly, the tendency to emphysematous overdistension of the alveolar air spaces seems to be a characteristic phase of the pathologic process. It is to be seen in parts of the lung parenchyma which show as yet no evidences of edema or of hemorrhagic extravasa-

tion. It is not caused by the mechanical presence of the injected material within the respiratory tract, for by the time the first symptoms of illness appear in the inoculated animals (six or more hours after the injection) the inoculated fluid is undoubtedly entirely absorbed. The cause is more likely to be the narrowing of the bronchial lumina due to congestion and edematous swelling of the lining mucosa. The presence of the profuse frothy mucoserous fluid within the lumen of the bronchial tree, also probably contributes to the respiratory difficulty. The development of these changes in the bronchi is coincident with the onset of asthma-like breathing and the presence of numerous moist râles on auscultation of the chest of affected animals.

Congestion of the lung parenchyma is usually patchy in distribution, as is the edema. In large and small areas, both the interalveolar tissue and the lumina of alveoli are filled with serum. Similarly, the hemorrhagic extravasations are patchy in distribution and involve the interalveolar connective tissue as well as the lumina of alveoli. These changes correspond with considerable accuracy to the lesions found in the lungs in the earliest human cases of influenza.

Blood Platelet Capillary Thrombi.—The minute intracapillary blood platelet thrombi constitute a significant and conspicuous feature of most of the experimental material that has thus far been studied. They have been found in the lungs of animals that were killed shortly after the development of the first manifestation of illness, and probably precede and are in part responsible for some of the features of the pathologic picture.

The occluded capillary loops are always widely dilated; the lining endothelium is swollen and often shows beginning proliferations; the lumen is occupied by a mass of blood platelets, scattered through which are sometimes a variable number of mononuclear and polymorphonuclear leukocytes. In the vicinity of such an obstructed capillary or minute arteriole, either edema or interstitial and intra-alveolar hemorrhages are usually present. But similar changes can sometimes be seen in capillaries within areas of lung parenchyma which show as yet merely some interstitial congestion and emphysema. The lesion has also been seen in the mucous membrane of the trachea of these animals.

Emulsions and filtrates of the lungs of animals showing such lesions have induced the experimental disease when injected into the trachea of other animals. The virus has thus been passed in series through several transmissions and in each transmission the capillary lesions have been seen. They, therefore, probably represent an essential and characteristic feature of the pathologic process in the earliest stages of experimental influenza.

Absence of Characteristic Lesions in Control Animals.—This belief is strengthened by the fact that we have not encountered this lesion of the lung capillaries in an extensive experience with human and animal pulmonary diseases. We have repeatedly produced pulmonary infections in rabbits by the intratracheal inoculation of various common pyogenic organisms such as the *Staphylococcus aureus*, *Streptococcus*

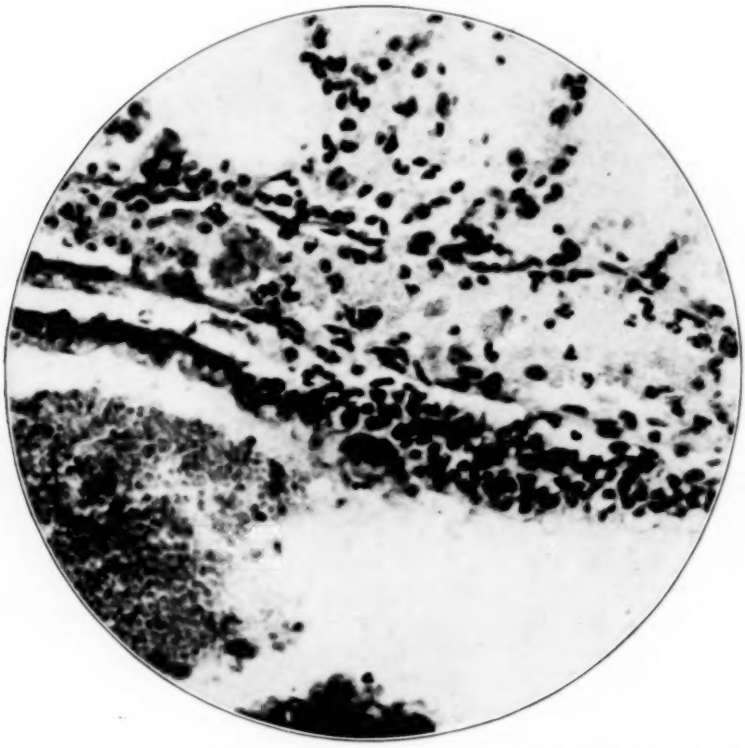

Fig. 4.—Peribronchial arteriole. The lumen of the small bronchus, which occupies the lower half of the field, is filled with red bloods cells. The adjacent arteriole which runs parallel to the long axis of the bronchus, is occluded with a blood platelet thrombus containing scattered polymorphonuclear leukocytes. The endothelium lining the arteriole, more especially on the side adjacent to the bronchioles, is very evidently in the process of proliferation. (×400.)

hemolyticus, pneumococcus, *Bacillus bipolaris* (distemper) and the *B. influenzae* of Pfeiffer, and have never seen anything remotely suggesting it.

Neither the capillary thrombi nor any of the other features of the experimental disease could be produced by the intratracheal injection of uninoculated culture material. In order to eliminate the possi-

bility that the pulmonary changes in our experimental animals might be due to a purely chemical action of the injected ingredients, the control culture mediums were employed after incubation at 37 C. for variable periods of time up to fourteen months.

Significance of the Blood Platelet Capillary Thrombi.—Changes similar to those seen in capillaries and arterioles in our animal lungs have also been described in the earliest stages of human influenza by Glaus and Fritzsche, Siegmund, Winternitz and Klotz. They have been searched for, though not found, by Marchand, Oberndorfer, Deitrich, Koopman and others who have also studied early examples of the disease. This may, in part, be due to the fact that in their human material the stage of secondary infection had already begun with its consequent obscuring of the primary pathologic lesions. It is more probable, however, that the greater frequency with which the capillary blood platelet thrombi occur in our experimental material is due to the fact that a much greater concentration of virus is introduced into the respiratory passages of the experimental animal than is responsible for infection in human beings.

As a result of a pathologic study of two fulminating cases of the disease, Oberndorfer was the first to voice the belief that the influenza virus produced a primary damage on the intima of small vessels. A similar viewpoint, based on a study of human material, has been expressed by Dietrich, Winternitz, Klotz, Glaus and Fritzsche, and Soerenson.

The lesions which we have been able to produce experimentally by means of influenza filtrates and influenza cultures leave little room for doubt that the virus possesses a peculiar affinity for the vascular endothelium. Numerous short stretches of capillaries and arterioles become widely dilated, apparently due to a complete loss in their normal tonus—and through their walls there occurs a great exudation of serum or a simultaneous extravasation of serum and red blood cells, which fills the interlobular and interalveolar connective tissue spaces and the alveoli in more or less sharply limited areas of vascular distribution. The blood platelet thrombi which become deposited in some of these dilated and damaged capillaries and arterioles are also to be encountered occasionally in parenchyma which is not as yet involved in any serous or hemorrhagic extravasation, so that they undoubtedly also represent an expression of the primary damage to the vascular endothelium. They are certainly not secondary to the other parenchymal changes.

Winternitz laid especial emphasis on the frequency with which necrosis of interalveolar septa occurs, and he regarded it as one of the characteristic effects of the disease. In the experimental material, necrosis and even rupture of interalveolar septum was occasionally encountered, but at the stage of the process at which the study was

necessarily made, this was not as yet a wide spread or conspicuous phase of the pathologic picture. In one of the fulminating cases of Glaus and Fritzsche, which probably represented a stage of the process somewhat later than our experimental disease, they call attention to the fact that though the necroses are numerous, the capillary thrombi are also to be seen outside of the necrotic areas. "In many instances," they state, "one can observe how the necrosis occurs in the immediate proximity of these thrombosed vessels." The experimental observations confirm this viewpoint that the capillary thromboses precede the necrosis and are not secondary to it.

Aplastic Character of the Inflammatory Exudate.—Perhaps the most striking feature of the microscopic picture in our experimental material and one which alone serves to differentiate it from any other type of pulmonary inflammatory process is the aplastic character of the alveolar as well as interstitial exudate. An occasional proliferated endothelial cell is encountered. But unlike any other type of pulmonary infection, no polymorphonuclear or other leukocytes are seen in the early stage of the process. The exudate consists almost wholly of serum or of serum and red cells. Although other pathologists have noted this unique feature of the process in early uncomplicated human influenza, Winternitz and his co-workers have especially emphasized the observation that "in the early stage, one of the most outstanding features is the absence of polymorphonuclear leukocytes in the reactionary process."

As soon as the secondary bacterial invasion occurs, an extensive leukocytic invasion rapidly changes this phenomenon and thereby completely obliterates the specific features of the pathologic picture. In the experimental animals such a transformation was observed to occur as early as forty-eight hours after the onset of the disease.

Yet even before this occurs, polymorphonuclear leukocytes are encountered in abnormal numbers within the blood platelet capillary thrombi. At a time when the alveolar and interstitial exudate, except for red cells, is still absolutely aplastic, many of the thrombi in occluded capillaries and arterioles are seen to be invaded by occasional proliferated endothelial cells and by polynuclear leucocytes in fair numbers. The aplastic nature of the other parenchymal changes would indicate that the virus of influenza does not possess the slightest chemotactic property. The appearance of leukocytes only within the capillary thrombi is, therefore, probably initiated by the positive chemotaxis exerted by the presence of the damaged endothelium within these vessels. In fact, their occurrence solely in the occluded vessels is evidence that damage has occurred at these sites and indicates that this damage, and not mere mechanical factors, is responsible for the blood platelet deposition.

Winternitz, Wason and MacNamara described a hemogeneous hyalin-like necrosis of the epithelium lining the trachea and bronchi, and, mainly for this reason, they likened the pathologic picture of the disease to that produced by the poisonous gases employed during the war. We have failed to observe this superficial necrosis in our experimental material, as have most other pathologists in their early examples of human influenza. Therefore, we feel that it is probably caused by a combination of the primary damage to the mucosa and the secondary infection and that it represents a complication rather than an essential feature of the primary pathologic process.

SUMMARY

The following pulmonary lesions were produced in rabbits by the intratracheal inoculation of Berkefeld filtrates of nasopharyngeal washings from early cases of influenza or of cultures of the filtrable punctiform bodies cultivated from such washings by Loewe and Zeman:

(1) Congestion, edema and small hemorrhages in the mucous membrane of the trachea and bronchi.

(2) Presence of a profuse, slightly blood-tinged, frothy, serous fluid in the lumen of the bronchi.

(3) Diffuse patchy distribution of red, jelly-like lesions throughout the lungs.

(4) Intense congestion of a large part of the intervening lung parenchyma and acute emphysematous overdistension of alveoli.

(5) Widespread exudation of serum and extravasation of red blood cells from the vessels, filling interstitial tissues and groups of alveolar air spaces.

(6) Aplastic character of this exudate.

(7) Aneurysmal dilatation of short stretches of capillaries and arterioles and sometimes closure of the lumen of these vessels at these sites by blood platelet thrombi.

(8) Tendency to early secondary invasion with pyogenic organisms, which then induce a rapid purulent infiltration, thereby completely obliterating the primary and specific picture of the disease.

These characteristics have all been observed in human influenza by pathologists who have had the opportunity to study the lungs of patients with fulminating disease who died within the first few days of their illness and before secondary infection had occurred. The lesions as they occurred in these early cases have been regarded as constituting a specific pathologic picture. Our experimental lesions correspond with considerable accuracy to those of human influenza and they cannot be confused with the changes produced by any other pathogenic organism either in human beings or in animals.

The unusual nature of the pathologic process in influenza is apparently due to the fact that the virus of this disease possesses a remarkable affinity for the vascular endothelium. The virus gains access via the respiratory passages, and is rapidly absorbed through the mucous membrane of the trachea, bronchi and bronchioles. Apparently, as a result of its peculiar endotheliotoxic property, it then rapidly calls forth a profuse outpouring of serum and red blood cells in patchy areas throughout the lungs.

Further evidence of this vascular damage is to be seen in the complete loss of tonus in many capillary loops and in the early occlusion of many capillaries and minute arteroles by blood platelet thrombi. This phenomenon, though observed in the lungs of some of the earliest human cases of influenza that were studied pathologically, can be regularly produced experimentally with influenza virus and influenza cultures and is of considerable pathogenetic significance.

THE MECHANISM OF THE DEVELOPMENT OF NON-BACTERIAL, CHRONIC CARDIOVALVULAR DISEASE *

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A fairly complete search through the literature reveals no accurate knowledge or satisfactory explanation of the pathologic process which is the basis of the progressive development of chronic cardiovalvular disease. By chronic cardiovalvular disease is meant a chronic, nonbacterial, nonrheumatic disease of a heart valve, or of valves, which is characterized at the necropsy by marked fibrosis of the valve cusps or flaps sometimes causing marked distortion or stenosis, at times with calcareous deposit in the valves, but unaccompanied by vegetations other than very small ones, such as are described in this paper.

The histologic changes in simple or verrucous endocarditis are well known, as are those of the terminal stage of the process which is usually, through improperly, termed "chronic endocarditis." The cause of the progressive changes in nonbacterial lesions of the heart valve, and the mechanism of these changes, is very imperfectly understood.

It will be necessary, before taking up this problem, to discuss the terminology and classification of acute and chronic diseases of the heart valves. Many of the older terms given to different types of cardiac disease have been found inappropriate in the light of recent knowledge. Many cases have erroneously been termed acute endocarditis where there was no acute inflammation of the endocardium. The term, however, which probably has been most abused is "chronic" endocarditis. This term should be discarded, as there is in all probability no disease of the heart valve which can be described as a "chronic" inflammation. The only conditions that should be termed endocarditis are those which are inflammatory in nature, and in which the etiology of the inflammatory lesion of the endocardium is known. These are bacterial, rheumatic and syphilitic endocarditis. As Libman suggests, the organism causing the bacterial endocarditis should always be included in the name of the lesion; such as "acute *Staphylococcus aureus* endocarditis."

In the same way, "chronic myocarditis" is usually improperly applied. Chronic inflammation of the myocardium is very rare, indeed. Most cases termed "chronic myocarditis" are conditions entirely different from this, such as myocardial weakness, interestitial fibrosis of the myocardium, either localized or diffuse, coronary artery disease, etc.

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* From the Laboratories of Columbia Hospital.

Libman [1] differentiates sharply between cases of valvular defect alone and cases of endocarditis occurring with or without a previous valvular disease. He describes a valvular defect as "a direct result of a previous disease process of the valve." The important point to be made clear is that a valvular defect is the result, or sometimes the end stage, of disease of a heart valve, and cannot, in any sense, be termed an endocarditis, acute or chronic. Libman tabulates the causes of valvular defects as follows:

1. Rheumatic endocarditis.
2. Syphilitic endocarditis.
3. Atherosclerosis.
4. Congenital defects.
5. Traumatic lesions.
6. A previous bacterial infection, with recovery.

He classifies the varieties of "endocarditis" (not valvular defects) as follows:

1. Rheumatic.
2. Syphilitic.
3. Bacterial.
4. Terminal (verrucous).
5. Indeterminate.

This terminology and classification is considered the best yet suggested. It is believed, however, that the term "endocarditis" should be eliminated entirely, and, in its place, the conditions should be termed acute or chronic cardiovalvular disease. It is probably too much to expect that the term endocarditis will be given up, but it seems certain that the term chronic endocarditis will be dropped. The term endocarditis is used herewith in connection with rheumatic fever and bacterial valvular disease, in order to conform with the present accepted terminology.

We are not concerned in this paper with bacterial infections of the endocardium, whether they are acute or subacute, or, as the latter is sometimes termed, chronic malignant endocarditis. These conditions have been described well by Schottmueller, Horder, Osler, Libman, Rosenow and others. The mechanism of the development of these lesions is also well understood, whether considered as starting from a bacterial embolus in the valve, or whether they start from bacterial implantation on the valve. Some phases of this mechanism, however, will be discussed later, as they have a bearing on the mechanism of the development of chronic cardiovalvular disease.

1. Libman, E.: A Study of the Endocardial Lesions of Subacute Bacterial Endocarditis, Am. J. M. Sc. **144**:313, 1912. The Clinical Features of Cases of Subacute Bacterial Endocarditis That Have Spontaneously Become Bacteria-Free, Am. J. M. Sc. **146**:625, 1913. Some General Considerations Concerning Affections of the Valves of the Heart. (Clinic of Dr. E. Libman, Mount Sinai Hospital, New York.)

Fig. 1.—Verruca on mitral valve in a case of acute rheumatic fever, showing beginning organization of hyaline thrombus deposit and reaction in valve beneath.

Our problem narrows itself to this: in what manner do chronic nonbacterial diseases of the heart develop, and what is the pathology and histology of this process? It is believed that the clue to the solution of this problem is to be found in the correlation of the results of the study of certain small excrescences found in a number of abnormal or diseased conditions of the heart at different locations on the endocardium, but most often on the valves. These conditions are congenital cardiac disease, so-called simple or verrucous endocarditis of rheumatic fever, so-called terminal verrucous endocarditis, and verrucous endocarditis in practically all cases of chronic cardiovalvular disease. These will have to be described separately, and it is also necessary to discuss bacterial endocarditis.

VARIETIES OF ENDOCARDITIS

Bacterial Endocarditis.—The macroscopic and microscopic characteristics of bacterial endocarditis are well known and need no further description. Reference can be made, in particular, to the articles of Libman.[1]

The vegetations, except in acute fulminating cases, are comparatively large and rough, being warty or cauliflower-like in appearance, or occurring as even larger, irregular masses. In cases such as acute pneumococcus endocarditis complicating a pneumonia, the vegetations may occasionally be small and beaded, smooth and glistening. The organism causing the lesion always can be demonstrated readily, however, in either smear, culture or section, thereby differentiating these cases from the verrucæ of acute rheumatic endocarditis.

In only a single group of bacterial endocarditis cases, namely, the bacteria free cases of subacute bacterial endocarditis, as described by Libman, are no bacteria found in the vegetations. Nevertheless, there can be no doubt that Libman has demonstrated that bacteria caused the lesions and these subsequently become bacteria free.

Bacterial vegetations are always friable, unless calcified, and even then, they are usually friable. They are made up of masses of blood platelet thrombus, mixed thrombus, bacteria scattered or in masses, and also sometimes of calcareous deposit. Degeneration or necrosis of the thrombus material often occurs. Organization takes place only to a slight or moderate extent at the base of the vegetation, except in Libman's bacteria free cases, where it may extend throughout the vegetation. In all other bacterial cases the surface of the vegetations is not covered by endothelium and it is usually not covered even in the bacteria free cases. Bacteria growing in the thrombus form almost the entire surface layer but the bacteria may also be found far beneath the surface.

Occasionally small beaded vegetations occur alongside of large ones in subacute bacterial endocarditis, which, if alone, might be confused

Fig. 2.—Verruca on mitral valve in a case of acute rheumatic fever. Larger than the one shown in Figure 1.

macroscopically with acute rheumatic endocarditis. Microscopically, they are easily differentiated, as they always contain bacteria. Bacterial vegetations, therefore, are merely infected thrombi on the valves.

Simple or Verrucous Endocarditis of Rheumatic Fever.—This condition is so well described by Aschoff in his textbook on Pathology, that only the necessities of this article justify personal observations of this lesion. This lesion is distinctive. The gross lesion is sufficiently characteristic so that acute rheumatic fever, or one of its associated conditions (such as chorea), can be diagnosed in practically every case in which this lesion is found. In a few hearts lesions have been observed that were so similar to those of verrucous rheumatic endocarditis that macroscopically it could not be decided definitely whether they were the lesions of rheumatic fever. In all of these cases, when a positive opinion could not be formed, subsequent study of the heart failed to reveal Aschoff bodies, which are the specific, microscopic, myocardial lesions of acute rheumatic fever and its allied conditions. In all hearts which were macroscopically regarded as representing a verrucous endocarditis of rheumatic fever, Aschoff bodies were found in the myocardium.

Rheumatic verrucous endocarditis appears grossly as a beaded line along the line of closure of the various valves. These beads vary in size from being barely visible to 2 or 3 mm. in both width and height. They may be either discrete or fused. When fused they form a continuous line on one or more of the valve flaps or cusps. When the beads are very small they give the line of closure of the valve a sandpaper-like appearance. The lesions are either colorless, or grayish white, rounded, smooth and glistening. They are never pedunculated but are always sessile. The verruæ are rather firm and tough, are not easily broken off from the valve and when picked off, a small portion of the superficial tissue of the valve invariably comes off with them.

Microscopic Appearance: The minute, beaded vegetations are composed entirely of an organizing, hyaline thrombus. The connective tissue immediately beneath the endocardium furnishes fibroblasts through which the thrombus becomes organized. The process of organization can, therefore, be regarded as beginning in these tissue cells. This area of actively growing connective tissue cells has all the characteristics of growing connective tissue elsewhere. More plasma is present between these cells than is found elsewhere in the valve. The valve about the base of the thrombus and, at times, the tissue throughout the valve, shows an inflammatory process. This process is an infiltration with mononuclear leukocytes, occasional plasma cells and polymorphonuclear leukocytes. The endothelium on either side of the thrombus, where it arises from the endocardium, shows a condition of active growth. There is apparently an effort on the part of the endothelium to

Fig. 3.—Terminal verrucous endocarditis; mitral valve; no organization of hyaline thrombus deposit and no reaction in the valve beneath it.

grow up over the thrombus. This new endothelium usually extends up on either side to a distance of from one-fourth to one-third of the surface of the thrombus. The verrucæ in the acute stage are infrequently completely covered by endothelium, though this always occurs with the older lesions. This observation is at variance with that of Libman, who claims that the endothelium rapidly grows over and completely covers the small verrucous vegetations.

In different vegetations may be observed varying numbers of hyaline thrombi encroached on by granulation tissue. Growing into the thrombus from its base, and from its side, the fibroblasts then attack these islands from their entire periphery and eventually convert them into a ball or whorl of granulation tissues, which become incorporated in the valve. This has an important bearing on observations which will be reported on later.

A careful search has been made by Rothschild and Thalhimer for bacteria and protozoa in the vegetations and myocardium in many cases of acute rheumatic fever. In no instance were any bacteria or protozoa found. It may also be stated here that no organisms were ever found in Aschoff bodies. This observation is of importance in relation to the contention of some authors that rheumatic fever is caused by a special type of streptococcus.

It could not be determined positively whether the minute thrombi of the vegetations were secondary to a lesion of the endothelial layer of the endocardium, or of the subendothelial layer. Beneath the very small lesions changes are present only in the most superficial layer of the endocardium. These changes are so superficial that they seem to indicate that the primary lesions are essentially endothelial and not subendothelial.

It is of interest to note that Aschoff bodies,[2] or Aschoff cells, were never found in the vegetations, in their base or in the valves. Attention should be called to the fact that emboli never arises from the vegetations in cases of acute rheumatic endocarditis, since the vegetations are never friable enough to break and form emboli. Where embolic phenomena occur in this condition the emboli must arise from thrombi situated elsewhere than on the heart valves, such as from an auricular thrombus.

Terminal Verrucous "Endocarditis."—Terminal verrucous "endocarditis" occurs in patients who die after a long, slowly progressing illness, such as carcinoma, tuberculosis, etc.

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2. In a study made by Rothschild and myself (Rothschild, M. A., and Thalhimer, W.: On the Significance of the Sub-Miliary Myocardial Nodules of Aschoff in Rheumatic Fever, J. Exper. M. **19**:417, 1914), a very careful search was made in the valves of rheumatic hearts for Aschoff bodies. We were, and are still, at a loss to explain their absence here and their presence in the specific lesions of the myocardium.

Fig. 4.—Terminal verrucous endocarditis; flat hyaline thrombus deposit on aortic valve. No organization of thrombus or reaction in the valve beneath it.

There are present upon the heart valves of many of these cases very minute, colorless or gray, rounded, glistening, firm verrucæ. They are usually smaller than those in rheumatic fever, fewer in number, scattered, and never form a continuous beaded line.

Microscopically these terminal verrucæ have identically the same structure as those caused by rheumatic fever, but there is no inflammatory reaction in the valve, either near the verrucæ or elsewhere. The small vegetations are formed entirely of hyaline thrombi, usually bare, but sometimes covered partially or even completely by endothelium. Either no organization of this thrombus is present, or practically none. There is no change in the valve beneath the verrucæ which is in any way related to the process on the surface of the valve. The small vegetative lesions have all the appearances of a recent process, without any accompanying inflammatory changes and with only proliferative changes in the heart valve.

A Special Type of Verrucous Endocarditis Found on the Valves of Nonbacterial, Nourheumatic Chronic Cardiovalvular Disease.—Verrucous "endocarditis" in chronic cardiovalvular disease is believed to be of common occurrence and yet seems to have been either comparatively unnoticed, or regarded as unimportant. I call attention to these lesions in the hope that others will verify the fact of their common occurrence and of certain structural valve changes associated with them.

On practically all thickened, fibrosed valves, careful inspection will reveal the presence of few or many minute verrucæ, grossly and microscopically similar in appearance to the very small lesions of terminal verrucous endocarditis. They are specially common on valves presenting marked stenosis, such as "buttonhole" mitral stenosis. In these extreme degrees of valvular defect the valve flaps are greatly thickened, very fibrous, usually uneven and often infiltrated with small or large amounts of calcium. Very often one or both places of junction of the two mitral flaps have a superficial, or deep, cracklike defect, which has somewhat the appearance of an ulcer. These cracks are at the ends of the "buttonhole" opening in the valve. The edge of these ulcer-like lesions is firm, irregular and slightly raised. The bases are rough and dull in appearance, as though composed of poorly nourished or degenerative tissues. On or near the edge of the cracks, as well as on the rounded valve edges, are found a few, or many small verrucæ. These verrucous lesions in their macroscopic and miscroscopic appearance resemble both rheumatic endocardial verrcucæ and terminal endocardial verrucæ, and have some of the characteristics of both. They are generally larger than the terminal, but not as large as the rheumatic lesions. They also are composed of hyaline thrombi, usually bare, but sometimes covered by endothelium. They show different degrees of

Fig. 5.—Small flat verruca on mitral valve in a case of chronic cardiovalvular disease. Organization is occurring and fibroblasts are scattered throughout the hyaline thrombus mass. The surface is covered by endothelium.

organization, from a small amount up to complete fibrosis. A slight or moderate grade of mononuclear cellular infiltration is quite constantly present at the base of the vegetation. This may be present elsewhere in the valve, but usually is not.

The more organized verrucæ very often revealed a whorllike arrangement of the newly formed connective tissue and some of the completely organized verrcuæ are made up of very dense fibrous tissue, with few flattened, densely staining nuclei. Areas of hyalin (possibly thrombus) are found in some of the verrucæ. Microscopically the structure of the valves is seen to be made up of dense, irregularly arranged fibrous tissue. The dense fibers of this tissue are, in general, parallel to the valve surfaces, but a wavy or even a whorllike arrangement of the fibers is often present. These whorls are found with special frequency in flattened knoblike projections of the valves near the verrucæ, and seem to be the result of the manner of organization of the verrucaæ. The central portion of the valve often contains areas of hyaline degeneration.

The cracks mentioned above are bare of endothelium, which stops at the edge. The base is made up of the fibrous tissue of the valve, with a layer of superficial degeneration, and here and there, small bits of hyaline thrombus. A considerable degree of calcareous deposit is usually present along the edge and in the base of the crack.

Nonbacterial Endocardial Vegetations in Congenitally Abnormal Hearts.—It is recognized that "endocarditis" commonly develops on valves of congenitally abnormal hearts. Necropsies have been performed in many of these cases and the cardiac abnormalities and gross appearance of the valves have been described carefully. Unfortunately, the microscopic structure of the valve lesions has seldom been studied. Bacteriologic investigations either have not been done at all, or have been unsatisfactory. Sufficient care has not been taken to rule out postmortem invaders of the heart's blood when positive postmortem bacterial cultures were obtained. Very few cases were studied clinically by means of blood cultures. Many of the important and most often quoted cases came to necropsy previous to, or during the early years of, the development of the science of bacteriology.

Nevertheless, quite a number of cases of "congenital heart disease" are recorded in the literature in which it has been proved that a superimposed acute or subacute bacterial endocarditis occurred. The heart valves have usually shown a chronic thickening and bacterial vegetative process. This fact directs attention to well known observations which are of importance. One is, that the valves of congenitally abnormal hearts are prone to become thickened and fibrosed. The other is that these compromised valves are susceptible to bacterial infections, just as is the case with all chronically diseased heart valves.

Fig. 6.—Verruca on mitral valve in a case of chronic cardiovalvular disease. Organization is almost complete, only two small unorganized areas of hyaline thrombus remain. The newly formed connective tissue has a whorllike arrangement. The surface is almost completely covered by endothelium. The vegetation is flattened and almost completely incorporated into the valve.

Attention can now be directed to certain organic changes in congenitally abnormal hearts and also to some personal observations of these changes.

A number of cases are on record in which endocardial thickening, or thickening of the intima of the large arteries which arise from the heart, has been observed at situations where abnormalities in the course of the blood stream through the heart have caused this stream to impinge on the endocardium or intima, or to put unusual strain on it. These thickenings have also occurred at places where slowing of the blood stream, or eddies in it, have occurred. Bacterial endocarditis has also been found at these situations. Illustrations of this are lesions (bacterial or nonbacterial) in the pulmonary artery opposite an open ductus arteriosus where the blood has impinged, or around the pulmonary opening of the ductus where the stream has been slowed and thrown into eddies.

In addition, I have had the opportunity to study several congenitally abnormal hearts where nonbacterial vegetative lesions were present on the valves.[3] To avoid repetition of what has gone before—the lesions bear a striking resemblance macroscopically and microscopically to the verrucæ of rheumatic endocarditis, terminal endocarditis and those observed on chronically diseased valves.

PRELIMINARY SUMMARY

The nonbacterial vegetations on the heart valves which have been described are formed of small thrombi on the valve. These lesions are verrucous rheumatic endocarditis, terminal verrucous "endocarditis" verrucæ on chronically diseased valves, and nonbacterial vegetations on the valves of congenitally abnormal hearts. It is believed that the same conditions which govern thrombus formation in blood vessels govern the formation of a thrombus on a heart valve. The underlying factors in thrombus formation are not understood perfectly, but a great deal of investigation of the condition has been made and the summation of our knowledge of the subject is best given in the conclusions arrived at by Aschoff:[4]

> So we see from all these experiments that the slowing of the blood stream and the alteration of the blood elements themselves, especially alterations of the platelets, are the chief factors in the production, not only of the static, but of toxic thrombosis, so far as we are concerned with thrombus formation in the flowing blood stream. In static and similar types of thrombi the slowing of the blood stream is of primary importance, while for the toxic varieties the changes in the blood elements have the dominating influence.

3. One of these cases has been quoted in Dr. Abbot's article on Congenital Heart Disease, in Osler's System of Medicine.

4. Aschoff, L.; von Beck, B., and de la Camp, O.: Beiträge zur Thrombosefrage. Leipzig. Verlag von F. E. W. Vogel, 1912.

Fig. 7.—Chronic cardiovalvular disease. Whorls occur in the fibrous tissue of the aortic valve.

The different types of chronic cardiovalvular disease and aseptic vegetations will be taken up separately, and a theory of the cause, development and end result will be advanced.

PROPOSED EXPLANATION OF MECHANISM OF DEVELOPMENT OF DIFFERENT TYPES OF CHRONIC CARDIOVALVULAR LESIONS

Verrucous Rheumatic Endocarditis.—There is sufficient evidence of inflammation in the heart valve first, to term this process "endocarditis" and, second, to believe that the vegetations develop secondary to an injury to the valve, caused by the infectious agent of rheumatic fever, which is at present unknown. Undoubtedly, fibrosis develops in the valve as a result of the inflammatory process. The inflammation is only moderate in degree and the amount of scar tissue which forms diffusely in the valve is only moderate in amount. The valve is made slightly thicker and less elastic as a result of these changes. The verrucæ become organized, then converted into fibrous tissue, and this also adds to the irregularity and loss of resiliency of the valve. Such a valve is less resistant to the strain which it must undergo in opening and shutting many times a minute and in withstanding the intracardiac pressure during the heart beat. Its lessened elasticity will cause it to open and close somewhat more slowly than normally and this will, therefore, cause slight slowing of the blood stream past the valve, and possibly, whirls or eddies in the blood stream. These two changes in the blood stream are conducive to thrombus formation. It is also conceivable that some unusual strain on the heart, and, therefore, on the somewhat compromised valve, might cause a minute injury to the valve, such as a microscopic tear in its endothelial covering. In the presence of a slowed blood stream this microscopic surface lesion would tend to add another factor toward inducing a minute thrombus, i. e., a verrucous vegetation, to form on the valve. The subsequent organization and fibrosis of this vegetation would cause further thickening and fibrosis of the valve. This would complete a vicious cycle consisting of recurring minute thrombi on the valve, very gradual thickening, with increasing susceptibility to further thrombi until a much deformed valve would result. During the process of the slow development of this valve defect, extending over many years, the valve and heart apparently might be performing their function in a satisfactory manner and no symptoms or physical signs be evident. Finally, when a seriously defective valve has developed the efficiency of the myocardium will become impaired and both symptoms and signs of chronic cardiovalvular disease will be manifested.

It is well known that recurrent attacks of acute rheumatic fever are prone to occur, and often these recurrences each add marked insult to the already damaged heart valves and hasten the development of a

Fig. 8.—Chronic cardiovalvular disease; mitral valve. Two, low, rounded projections of surface with whorllike arrangement of connective tissue of valve beneath each projection.

valvular defect. We must note that repeated rheumatic inflammations of the valves are undoubtedly sufficient, without any other agency, to produce even the severest grades of valvular disease. It is, therefore, not necessary after repeated attacks of rheumatic fever have occurred, to hypothecate additional factors for causing the progress of sclerosis in the heart valves. The surface lesions in cases of acute rheumatic endocarditis, however, present so many points of similarity to lesions on sclerosed valves, which are not rheumatic in orgin, that this similarity suggested the idea of the possible significance, cause and effect of all verrucous-like, nonbacterial vegetations in the development of chronic cardiovalvular disease.

It must be recalled that an appreciable number of cases of chronic cardiovalvular disease occur in adults who have a history of only a single attack of acute rheumatic fever occurring in childhood or early life. These chronic valve lesions are attributed by clinicians to the previous attack of rheumatic fever. The explanation has not been given of how the single trauma to the heart valves long before, causing no symptoms for many years, may finally be the cause of marked valvular defects and their consequences. One attack of acute rheumatic endocarditis produces a comparatively slight valvular lesion. This may give rise to no immediate symptoms or heart murmur. It is evident that the valve defect, which is the final stage of the process, has developed slowly. The cases under discussion give no history of subsequent attacks of acute rheumatic fever or other infectious diseases to account for the development of the severe valve lesion. The explanation given here of recurring, minute verrucæ, always followed by fibrosis, would satisfactorily account for the progressive change from a slightly damaged valve to a markedly damaged one years later.

Verrucæ in Chronic Nonbacterial, Nonrheumatic Cardiovalvular Disease.—These lesions must have some significance, and some effect. Theoretic considerations, quite similar to those already stated, might also apply here. Some general toxic or some distant infectious process might result in a primary trauma to a heart valve, such as bacterial toxins from a serious pneumonia, repeated attacks of tonsillitis, the virus of scarlet fever, etc. Thickening of the valve follows, and these thickened valves have been found to be free from bacteria. Thus, the process of valve thickening can be regarded as nonbacterial in orgin. The thickened valve is more susceptible to both normal and unusual strain. Microscopic lesions form, followed by verrucæ, and these, in turn, by fibrosis. Following this, the sequence of progressive changes may occur in the same manner as has been described as possible after a single attack of acute rheumatic fever. This may eventually produce marked stenosis with a shelflike formation at the line of valve closure.

Cardiovalvular Lesions in Atherosclerosis.—Fibrosed, thickened and stenosed valves, found in general atherosclerosis can be explained similarly. The unusual amount of calcareous deposit in these cases is undoubtedly part of the process of atherosclerosis, probably initiating the valvular lesion and undoubtedly contributing markedly to its progression.

Aseptic Endocarditis and Chronic Cardiovalvular Disease in Congenitally Abnormal Hearts.—Congenitally abnormal hearts, which at necropsy show thickening and fibrosis of their valves, usually show no inflammatory reaction in the valves. The thickening is similar to that found in chronic valvular defects in adults. This does not include those with a superimposed bacterial endocarditis.

It must be granted that abnormal openings in a heart, or stenosis of its valves, result in one or several occurrences, such as, slowing of the circulation in the heart, whirls or eddies in the circulation, direct impinging of the blood stream on abnormal endothelial sites, etc.

A heart of this type is working under a strain. This is exemplified clinically by evidence of cardiac insufficiency occurring more easily after muscular activity in persons who have congenitally abnormal hearts than in normal persons. Poor or retarded physical development in children with congenital hearts is well known, and is another evidence of the inefficient cardiac mechanism. Such a heart and its valves are undoubtedly abnormally susceptible to a strain.

One can only consider hypothetically the possible result of this susceptibility to strain and of the abnormal course of intracardiac circulation and attempt to correlate it with the findings in other similar conditions. A few data of the effect of abnormal circulation and slowing of the circulation in the more common types can be brought forward before passing on to the theoretic considerations. A number of cases are on record in which, in aortic insufficiency, valvelike structures similar to the valves in the veins, developed on the interventricular septum below the aortic valves. This is the region where the regurgitated blood passes back through the aortic ring and impinges on the septum. Also, thrombus formation, due to slowing of the circulation because of chronic cardiovalvular disease is not uncommon in the auricular appendages. These appendages, because of their location, are more likely than any other structure to accommodate a slowed circulation or eddies in the circulation. These lesions are marked evidence of the effect of abnormal intracardiac circulation and slowing of the blood stream.

It would seem, then, hypothetically, that the following is possible: Congenital cardiac anomalies may cause the valves to be under an unusual strain from time to time. Minute, endothelial breaks, cracks, or damage may result. After these changes have occurred, fibrosed

valves may develop gradually in the manner and by the mechanism already described. Even larger vegetations may occur than those found in simple chronic valve disease. The reason may be that in congenital hearts the circulation is more abnormal, slower, and conducive to the development of larger vegetations.

Terminal Verrucous Endocarditis.—These lesions can be considered to give the clue to the significance of similar valve lesions found in other conditions, and described above. The verrucæ, which are terminal, are composed also of a hyaline thrombus and would seem to be induced both by slowness of the circulation, as vitality diminishes and death approaches, and, in some cases, by an increased coagulability of the blood. Death usually occurs before these thrombi can become organized.

SUMMARY

There is no satisfactory explanation as to why a slight nonbacterial damage to a heart valve during childhood gradually progresses and years later results in a severe chronic nonbacterial cardiovalvular lesion. The etiology of many of these chronic lesions is attributed by some observers to the direct action of bacteria. This is undoubtedly erroneous. They are entirely different from the lesions of bacterial endocarditis. They, however, may be caused indirectly by bacteria through the effect of toxins.

The cause of the chronic valvular lesion in a case such as the following is not at the present time explained. There is either no history of an original insult to the heart valve, or there is a history of a single insult in childhood or youth. No subsequent symptoms of cardiac disease developed, and also, no heart murmurs, or only very slight murmurs. For many years there are no symptoms or signs of a lesion of the heart valve. Then, either slight or mild cardiac symptoms are manifested, at which time a heart murmur is found, or, no heart symptoms being present, the murmur is discovered during a routine physical examination. After this there is a more rapid progression of the heart lesion and the heart symptoms.

The question which suggests itself is, why has the lesion become manifest at this time, and what has occurred to the heart valve in the interim between the original insult to the valve and the later development of the valve lesion? The following argument is presented as a possible explanation of what has occurred: There was an original insult from one or more of the following diseases: scarlet fever, measles, tonsillitis, pneumonia, etc. The best evidence indicates that the slight cardiovalvular injury which occurs during these diseases is not caused by a deposit of bacteria in or on the valve. These lesions are, therefore, nonbacterial. (The occasional case of frank pneumococcus endocarditis

and other cases of bacterial endocarditis are not being considered here.) The nonbacterial process in the valve resulted in slight or mild fibrosis. The change in the valve was not serious enough to impair the heart function and cause heart symptoms; it may not have been even sufficient to have caused heart murmurs. This slightly damaged valve, however, did not have the resiliency, elasticity and reserve of a normal valve. The ordinary work of the heart put a strain on it. With the slight thickening of the valve a slight abnormality of the circulation over and around the valve occurred, which resulted in slight whirls or eddies, or slight slowing of the blood stream. Activities such as heavy lifting, or exercise, may have resulted in so much strain that a microscopic damage, which would not happen normally, was inflicted on the endothelium of the valve. At the site of this damage a minute thrombus was deposited. The whirls in the circulation about the valve, or the slight slowing of the blood stream, helped in the formation of this thrombus. This thrombus is the aseptic, verrucous, endocardial lesion or vegetation described herein. This verrucous vegetation became organized, then fibrosed and incorporated in the valve, adding to its thickening and fibrosis. This process still further lessened the elasticity, resiliency, etc., of the valve and rendered it more liable to subsequent minute injuries, verrucæ, and the result of organization of these verrucæ. Thus, a vicious cycle is completed, each minute injury and its repair rendering the valve more susceptible to further injury.

It is a common observation that mild degrees of thickening in the heart valve are found at necropsy, which have caused no murmurs or heart symptoms during life. Therefore, it is conceivable that the progressive change in the heart valve, which has been hypothecated above, gives rise to no heart murmurs or heart symptoms until a certain stage is reached. By that time quite a marked change in the valve is present. This markedly changed valve is especially susceptible to injury, and after this stage occurs, further progress in the lesion is more rapid. With the deformity or defect in the valve which eventually develops, the function or mechanism of the heart becomes affected and cardiac symptoms appear.

The manner in which a cardiovalvular defect eventually causes sufficient disturbance in myocardial function to precipitate signs or symptoms of myocardial insufficiency is not yet completely understood. Some subjects may go for years with a marked mitral stenosis and a perfectly compensated heart. Some subjects with no lesions of the heart valves may die from myocardial weakness due to one of many causes, such as, coronary artery disease, so-called cardiac rheumatism, toxemia of a severe infectious disease, etc.

It would seem that a valvular defect, even a serious one, if the myocardium has not also suffered damage, in many cases exists for

a long time before the interference with the cardiac function which follows causes insufficiency of the myocardium. There is great need for investigation of the manner in which chronic valvular defects cause deleterious functional and organic changes in the myocardium.

The evidence which has been presented to explain the progress of chronic, nonbacterial cardiovalvular disease is not necessarily conclusive, and it might be considered that the hypothesis has not been proven. All stages of the progress in these valve lesions are not available for study, but the similarity of the verrucous lesions in all the conditions described strongly indicates that a simple, fundamental process is the basis of all of them. This process seems to be an attempt at repair. It is evidently an imperfect attempt, such as occurs in arterial thickening in atherosclerosis. It is, therefore, another imperfect adaptation of the protective processes of nature. The repair of the heart valve results in fibrosis, lessened resistance to strain, more damage and consequent progress of the vicious cycle which has been established. In some cases even marked stenosis of the valve may result. This is an imperfect result of repair by nature, just as an aneurysm which occurs in atherosclerosis is the result of an imperfect repair. Other instances of the result of an imperfect adaptation of nature for the purpose of repair, are thrombosis in a blood vessel and its sequels, stenosis of the coronary artery in atherosclerosis, etc.

It is hoped that these hypothetic considerations, in spite of their possible incompleteness or imperfections, may direct attention to the processes described, and if the hypothesis is not justified by subsequent observation, that it may stimulate other investigations of the cause of development and progression of chronic cardiovalvular defects.

BRONCHOSPIROCHETOSIS IN CHINA*

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Bronchospirochetosis was first discovered by Castellani in 1905 in patients seen in Ceylon. The spirochetes which he found to be the causative agents of the disease were described by him in 1907 under the name of *Spirochaeta bronchialis*. About the same time Bertarelli and Volpina noted spirochetes in the sputum of persons suffering from heart disease, while Rona found similar organisms in cases of pulmonary gangrene. Since then instances have been reported from many localities. Lurie [1] recorded the presence of the disease in China, although the first and only published case history I have been able to find is that of Lee [2] from Wusih.

In view of the widespread incidence of bronchospirochetosis in Europe, North America and in parts of Asia (Ceylon, Philippines and Siam), I have been surprised to find records of the infection almost wholly lacking for China. In collaboration with Dr. C. McA. Wassell I started an investigation of the subject at the Church General Hospital, Wuchang, among patients suffering from hemoptysis, and discovered that the percentage of cases with bronchospirochetidial involvement was markedly high. Examination of suspected cases in other localities in China has revealed a similar condition.

Etiology and Description of the Parasite.—The disease is due to infection with a spirochete known as *Spironema bronchiale*. The infection has been referred to as "Castellani's bronchitis," "bronchopneumonial spirochetosis" and "bronchospirochetosis." The organism is polymorphic, with size variations of from 5 to 25 microns in length and from 0.2 to 0.3 microns in width, depending, in part, on the stage of development. Typical individuals have acuminate ends and from five to seven coils. Thus the organism as seen may be thick and short with few undulations or it may be thin and delicate with several coils. Since the short forms with few coils represent stages that have recently arisen from division of the parent organisms they are less apt to have pointed extremities than longer individuals. The organism may be viewed either in fresh smears with dark-ground illumination

* Contribution from the Parasitology Laboratory, Department of Pathology, Peking Union Medical College. Read before the Peking Branch of the China Medical Missionary Association and the Faculty Medical Club of the Peking Union Medical College, Nov. 23, 1921.

1. Lurie, G. A.: Notes on "Castellani's Bronchospirochetosis," with Report of a Case, J. Trop. M. & Hyg. **18**:269, 1915.

2. Lee, C. M.: Bronchospirochetosis, with Report of Case. China M. J. **32**: 332, 1918.

or in stained preparations. I have found a 2 per cent. aqueous solution of gentian violet well suited for such staining. In many stained organisms multiple division forms (coccoid bodies) are seen. These are believed to represent the infective stage and are thought to be transmitted by droplet spray in coughing and expectoration.

The life history of *Spironema bronchiale* has been worked out definitely by Fantham [3] who finds it to be a distinct species. No intermediate host is required. Moreover, Chalmers and O'Farrell [4]

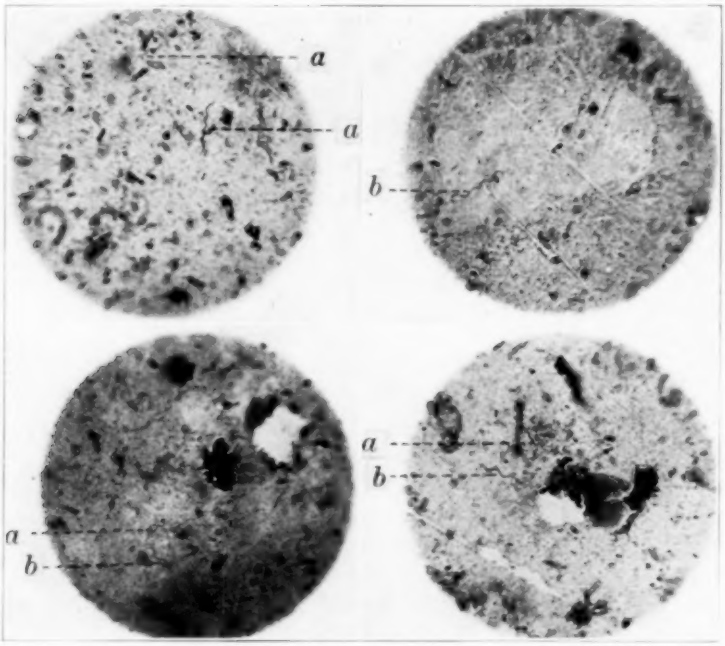

Fig. 1.—a, Vegetative organisms. b, Division forms. Note clear spaces between chromatin areas. ×720.

have shown by experimental infection of man and monkeys that this is the actual causal agent of bronchospirochetosis.

The diagnosis is made by examining the sputum in a suspected case and finding the organism, *S. bronchiale*, which may be differentiated

3. Fantham, H. G.: Spirochaeta Bronchialis, Cast. 1907, together with Remarks on the Spirochaetae of the Human Mouth. Ann. Trop Med. & Parasitol. **9**:391, 1915.

4. Chalmers, A. J., and O'Farrell, W. R.: Bronchial Spirochetosis, J. Trop. M. & Hyg. **16**:329, 1913.

from the buccal spirochetes by ascertaining (1) that it comes from the exudate of the trachea or bronchi, and (2) that it is not associated with the fusiform bacilli of Vincent's angina. Thus far, aside from size, actual morphologic differences from the mouth spirochetes have been difficult to demonstrate.

The disease may be simple or it may be complicated with pneumonia, pulmonary gangrene, empyema, tuberculosis of the lungs, moniliasis, paragonimiasis or rhinitic spirochetosis. While a certain proportion of cases in China will be found to be free from complications, a large share of them will probably prove to be primarily cases of pulmonary tuberculosis with a complication of bronchospirochetosis. In either instance it is extremely important to examine for these spirochetes the sputum of all persons giving a history of hemoptysis. If the spirochetes is found to be the primary agent of the disease, relief is easily effected. If the disease is complicated by some other infection, then spirochetosis can be eliminated, leaving the physician free to treat the primary agent of the disease.

Bronchospirochetosis may manifest itself as an acute attack or it may be chronic or subacute in its nature. In acute cases a chill develops, then fever, which, according to Castellani, seldom exceeds 39.5 C. This lasts for from two to eight days, during which time the patient coughs almost continuously and complains of pains all over the body. The expectoration is scanty, mucopurulent, very seldom containing traces of blood. This type is not likely to be found often in clinics in China, since the patient is reluctant to consult the physician until Chinese medications have been found ineffective. While arsenicals produce rapid relief, the clinical symptoms may disappear even without treatment.

In the subacute type the general symptoms are similar to those of the acute type, but there may be hemoptysis and bronchitis, with slight crepitations.

In the chronic type the disease may have been slow and insidious in onset, or the patient may give a history of previous acute attacks. When he comes for treatment he has a chronic cough, the sputum is mucopurulent, often bloodstreaked, while in many instances there is considerable hemoptysis. There may be moist or dry râles or consolidation areas.

In many cases there is a daily rise of temperature, sometimes reaching as high as 40.5 C. This is the usual type of patient to be dealt with in China, who will present himself at the tuberculosis clinic. In most instances rest and treatment with liquor potassii arsenitis (Fowler's solution), cacodylates, arsphenamin, or neo-arsphenamin, will bring about rapid recovery and apparent cure.

Cases of lung gangrene, empyema, fetid bronchitis and rhinitis are on record, in which *Spironema bronchiale* or a similar organism has been the only pathogenic body isolated, but such instances are rare compared with the usual chronic type.

Preliminary inquiries have revealed the presence of bronchospirochetosis in the following centers in China: Amoy, Nanking, Wusih, Wuchang, Pao Ting Fu and Peking.

Through the kindness of Dr. J. P. Maxwell I can report three cases of simple bronchospirochetosis from Amoy, Fukien Province, with no microscopic evidence of tuberculosis. Two of the patients were Northern soldiers, while one was a native of Fukien Province. They were probably all of the chronic type, with a variable amount of sputum, often streaked with blood. Treatment with tonics and potassium iodid was helpful "as far as immediate results were concerned."

Out of five cases found positive for tubercle bacilli in the sputum in the Nanking Hospital in September, 1921, four were also positive for *Spironema bronchiale*. These were all chronic cases. Dr. Hutcheson has recently found several cases of simple bronchospirochetosis.

Lee's record [2] for Wusih was that of a chronic case, with a history of hemoptysis. Repeated examinations for tubercle bacilli were unsuccessful. Sodium cacodylate per orem brought about rapid recovery.

In September, 1921, Dr. J. H. Wylie of Paotingfu brough me smears of sputum which contained *Spironema bronchiale* in large numbers. Several examinations by Dr. Wylie revealed no tubercle bacilli. On entering the hospital, the patient had marked hemoptysis, which recurred every three or five days. He was quite anemic. He remained in the hospital about three weeks, during which time he was given three intravenous injections of neo-arsphenamin, the first consisting of 0.45 gm. and the second and third of 0.6 gm. each. After the third dose his sputum was free from spirochetes. Other cases have more recently come to Dr. Wylie's attention, including one with a history of syphilis and one in which death resulted from pulmonary tuberculosis.

I have more recently been able to confirm the presence of the parasite in patients in Peking giving similar clinical histories.

Through the kindness of Dr. C. McA. Wassell I have had an opportunity to study several cases of bronchospirochetosis from the Church General Hospital, Wuchang. Five of these cases have been available for analysis and are briefly presented here.

REPORT OF CASES

CASE 1.—Chronic Type (Chart 1).

History.—Chinese soldier, aged 25, complained of profuse expectoration, about 300 c.c. per day, blood streaked; loss of weight; painful cough and fever.

Family history—negative. One friend died of hemoptysis recently. At 11 years of age he had profuse nose bleeding. At 20 he had tertian malaria. At

21 he had gonorrhea. June, 1920, he had blood-tinged expectoration and was treated by a native doctor. He has not been well since. He has had recurrent attacks with fever, expectoration, but no night sweats. Two months previously he suffered exposure on a long march, resulting in coryza and profuse expectoration. This condition prevailed up to the time of his examination.

Physical Examination.—On admission to the hospital the patient's temperature was 38.5 C.; pulse 76 and respirations 20. He was physically weak, hollow eyed, with cold perspiration all over the body. His mind was clear; eyes reacted normally, and skin was of a good color. Nose, lips, palate and pharynx were slightly congested. The teeth showed some caries as well as pyrrhea. Neck glands were slightly enlarged in left submaxillary region but without fluctuation. Larynx was without tracheal tugging. Chest was without deformation and with normal respiration. On percussion a dulness was demonstrated in the right axilla above the liver and in the right scapular area. The right lung above scapula showed coarse crackling râles, which were quite audible on soft coughing. Fine moist râles were found in the right midaxillary line between the eighth and ninth ribs. The bones and extremities were normal. Reflexes, normal.

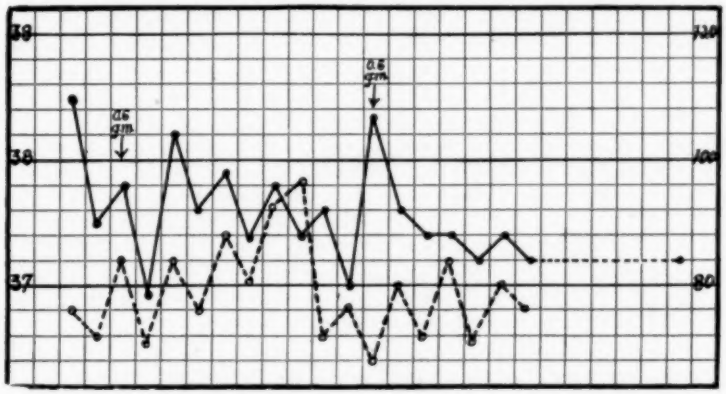

Chart 1.—Wuchang Case 1. Simple chronic bronchospirochetosis.

Laboratory Data.—The sputum was negative for tubercle bacilli after repeated examinations, but was positive for spirochetes after rinsing of the mouth. The feces were positive for ascaris, ancylostoma and cysts of *Endameba dysenteriæ* and *E. coli.* The urine gave an acid reaction, was orange in color and had a specific gravity of 1.030. On entrance the blood was positive for *Plasmodium vivax*, showed a red count of 4,450,000 and a white count of 12,700, with 75 per cent. hemoglobin. Eosinophils were 12 per cent. A tentative diagnosis of bronchospirochetosis and tertian malaria was made.

Clinical Data.—On the day after admission, the patient was treated intravenously with 0.6 gm. of neo-arsphenamin. The temperature remained between 37.5 and 38.2 C. for five days, although there was a general note of improvement. On the seventh day the temperature rose to 38.5 C., whereupon a second administration of neo-arsphenamin was made (0.6 gm.). The temperature then returned to normal and remained so until the patient was discharged. Blood examination on the fifth day showed a slight increase in reds (4,864,000) and a decrease in whites (9,100), with a marked reduction in eosinophils (6.3 per cent.). The reds increased to 6,000,000 on successive examinations, while the white count was reduced to 7,000. The eosinophils remained high until clinical symptoms disappeared. On the eighth and successive days the spirochetes were

not found in the sputum. At the same time the lungs became clear, the râles and dulness disappeared and the general condition of the patient was markedly improved. He was discharged on the ninth day and three months later showed no recurrence.

CASE 2.—Chronic Type (Chart 2).

History.—Chinese farmer, aged 18, complained of dyspnea, cough, expectoration and at times hemoptysis; also ulcers of feet due to wearing grass shoes. Family history negative. No disease of childhood, except chronic profuse expectoration since 9 years of age, with hemoptysis at 12 years.

Physical Examination.—On admission to the hospital, the patient's temperature was 37.4 C., pulse 100, respirations 24. He was of ordinary build and fairly well nourished. Intelligence good; speech alert. Skin good, intact except for ulcers on feet. Membranes of both nares red, inflamed. Lips inflamed and feverish. Pharynx without exudate, tonsils normal. Teeth and gums good. Palate normal, no laryngeal tugging. Glands in neck enlarged on both sides along sternocleidomastoid muscles. Thyroid somewhat enlarged; no pulsations. Chest full, normal. Dyspnea. Right axillary space dull to percussion. Breath sounds over right axillary space hard and tubular. Few fine râles under right nipple and over right base along spinal border. Extremities normal except for ulcers on feet.

Laboratory Data.—Sputum negative for tubercle bacilli after repeated examination, but positive for spirochetes. Feces positive for ascaris. Urine, a light straw color, acid in reaction, with a specific gravity of 1.005; positive for traces of sugar. On entrance, the blood was negative for malaria, with a red count of 4,000,000 and white count of 8,700. Eosinophils numbered 18 per cent. An admission diagnosis of bronchospirochetosis and ulcer of the foot was made.

Clinical Data.—Soon after admission the patient's temperature rose to 38.1 C., then dropped to 36.8 C. On the tenth day, 0.45 gm. neo-arsphenamin was administered intravenously. The temperature was reduced and remained near normal until discharge, twenty-six days after entrance. Spirochetes disappeared from the sputum two days after administration of the arsenical and did not reappear. Meanwhile the blood picture improved (red count 4,700,000, white count 6,800) although the eosinophilia remained pronounced (from 16 to 17.5 per cent.). The patient was discharged as improved.

CASE 3.—Chronic Type.

History.—Chinese soldier, aged 25, complained of weakness, profuse expectoration, bad cough, hemoptysis. Family history negative. Patient had no illness up to the age of 24 years, at which time he had hemorrhages, cough and weakness. This continued intermittently, becoming more pronounced after extra exertion.

Physical Examination.—On admission to the hospital the patient's temperature was 36.0 C., pulse 90 and respirations 20. His general appearance was normal. Skin negative. Nose slightly inflamed in left turbinal area. Lips, teeth, palate, neck and larynx all negative. Chest with moist bubbling râles along both borders of sternum and at left apex. Extremities and bones negative.

Laboratory Data.—The sputum was negative for tubercle bacilli on successive examinations but was positive for spirochetes. The feces were positive for trichuris. Urine was negative. On admission the red cells numbered 6,100,000 and the white cells 5,000. Eosinophils were 20 per cent. A tentative diagnosis of bronchospirochetosis was made.

On the day after admission when a rise in temperature was observed, the patient was treated with 0.45 gm. neo-arsphenamin. This caused improvement so that on the fourth day the sputum became negative for spirochetes, and the eosinophilia was reduced one-half. The general improvement of the patient was soon observed. He left the hospital on the sixth day, but returned two days later for a second administration of 0.45 gm. neo-arsphenamin. He was apparently helped.

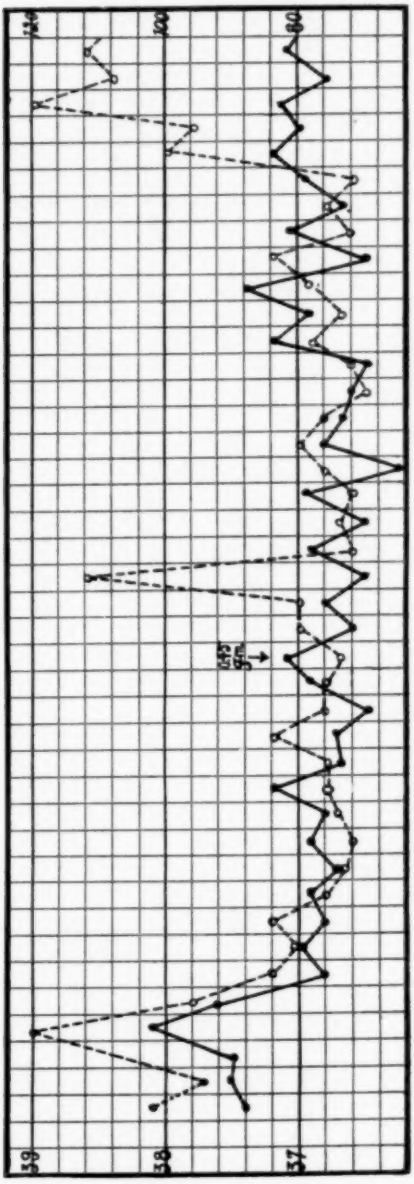

Chart 2.—Wuchang Case 2. Simple chronic bronchospirochetosis and ulcerated foot.

CASE 4.—Pulmonary tuberculosis complicated by bronchospirochetosis (Chart 3).

History.—Chinese soldier, aged 24, complained of expectoration and dyspnea. Family history negative. Past history with record of smallpox, malaria and gonorrhea. Two months previously patient noted pinkish sputum and felt ill. He had night sweats and afternoon fever. He became weaker day by day with increased dyspnea. Stool was fluid since attack.

Physical Examination.—On admission the patient's temperature was 37.8 C., his pulse 126, and his respiration 26. Nutrition poor; malaise. Anemia pro-

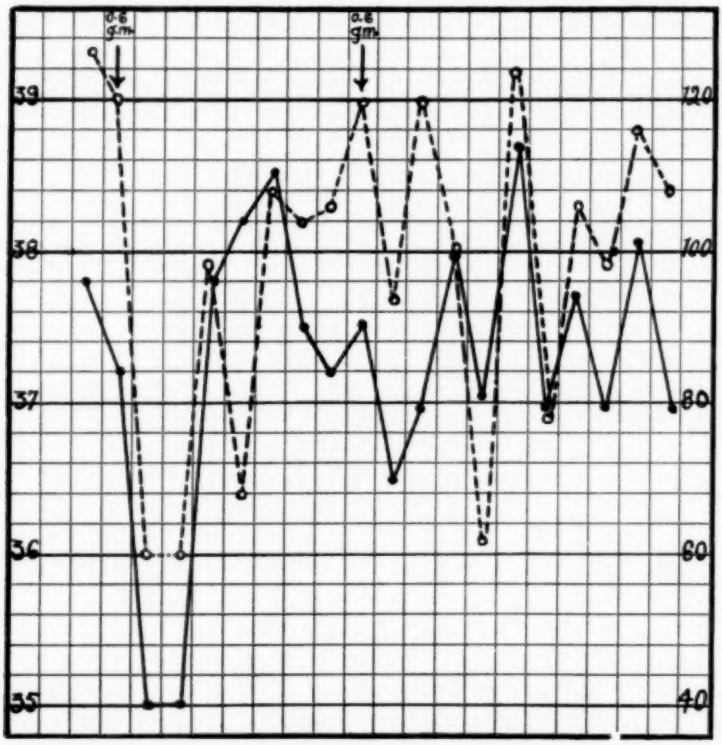

Chart 3.—Wuchang Case 4. Pulmonary tuberculosis complicated by bronchospirochetosis.

nounced in eyes, lips, skin and gums. Neck glands hard; no enlargement or pulsation. Tactile fremitus decreased in right axilla. Dulness over a triangular area under right axilla and behind this area. Moist râles above and between these areas. Extremities and bones negative. Reflexes normal.

Laboratory Data.—The sputum was positive for tubercle bacilli and for spirochetes. Feces were positive for ascaris and for *Endameba coli* cysts. Urine was yellow, acid in reaction, of a specific gravity of 1.010, with a slight trace of sugar. The red count was 4,400,000 on admission while the white count was 10,500. Eosinophils were less than 1 per cent. A tentative diagnosis of pulmonary tuberculosis and of bronchospirochetosis was made.

Clinical Data.—Two days after admission, 0.6 gm. neo-arsphenamin was administered intravenously. This was followed by profuse sweating and a chill, with a reduction of temperature to 35.0 C. After two days it mounted to 37.8 C. On the sixth day, a second administration of 0.6 gm. neo-arsphenamin was given, which was followed by a chill. Temperature remained irregular up to the time the case left the hospital. The sputum was negative for spirochetes after the fifth day but remained positive for tubercle bacilli. The red cells rose to 5,745,000 and the white cells were reduced to 6,700 after one week's time, but the general condition of the patient did not improve.

CASE 5.—Pulmonary tuberculosis complicated by bronchospirochetosis.

History.—Chinese cloth-weaver, aged 29, complained of cough, tightness in chest, dizziness, borborygmus, fever and pain in right breast. One sister and an intimate friend gave histories of hemoptysis. Diseases of childhood were confined to malaria and epistaxis. A year ago the patient had coma and numbness of the extremities, followed by dyspnea and dizziness about once a month. Patient denied having night sweats or afternoon fever or any exposure. Three months ago he had chills and fever followed by cough and sore throat. A white mucoid expectoration developed and a month later blood was found in the sputum. This continued intermittently until he entered the hospital.

Physical Examination.—On admission the patient's temperature was 38.4 C., his pulse 88, and his respirations 20. He had a well developed body, was well nourished, although slight anemia was evident. The lips were dry and feverish. Gums showed anemia. Tonsils, palate and pharynx were negative. No enlarged neck glands. Dulness in right lung near scapula. Râles were noted both on expiration and inspiration. Extremities were normal. Reflexes, normal.

Laboratory Data.—The sputum was positive for spirochetes on admission and was later found to contain tubercle bacilli. The feces were positive for ascaris. The urine was yellow, gave an acid reaction, had a specific gravity of 1.018 and showed a slight trace of sugar. The red cell count was 4,000,000 and the white cell count was 12,000. Eosinophils were less than 1 per cent. A tentative diagnosis of pulmonary tuberculosis and bronchospirochetosis was made.

Clinical Data.—The day after admission, the patient was given 0.6 gm. neo-arsphenamin, which was followed by a chill and profuse sweating. For the next three days the temperature ranged from 37 to 38 C. On the sixth day a second administration of 0.6 gm. neo-arsphenamin was given, which was without marked reaction. The spirochetes disappeared from the sputum two days after the first injection of neo-arsphenamin. The blood picture on the sixth day showed 5,400,000 red cells and 6,900 white cells with no increase in eosinophils. On the eleventh day the temperature and other symptoms showed such improvement that the patient asked to be dismissed.

DISCUSSION

A survey of the Chinese cases of bronchospirochetosis indicates two things. In the first place, a certain proportion of the subjects have pulmonary tuberculosis as a primary infection with a secondary spirochetosis. Secondly, cases of simple bronchospirochetosis are usually of the chronic type, giving a history of recurrent cough and hemoptysis for a period of from one to ten years. They differ markedly, then, from Chalmers and O'Farrell's experimental case [4] and from the cases cited by Bloedorn and Houghton.[5] In Chalmer's case the infection was under observation from the day of its inception. In each of

5. Bloedorn, W. A., and Houghton, J. E.: Bronchial Spirochetosis, J. A. M. A. **76**:1559 (June 4) 1921.

Bloedorn and Houghton's cases only a few days elapsed from the time the patient noticed the acute attack until he came to the hospital for treatment. In simple acute cases the picture is uncomplicated by other activating agents of disease. The observations are easily made and the symptoms are readily attributed to the single infective agent. These cases are also easily studied from the temperature graph.

Chinese cases are not so readily reduced to simple formulas. Granted that acute attacks of bronchospirochetosis are not uncommon among the Chinese, the fact that the patient in many communities comes to the hospital as a last resort means that the case has run a considerable course and has probably recurred several times before the physician has an opportunity to observe and treat it. The temperature in such chronic cases is lower and less regular than in acute cases. When the primary infection is pulmonary tuberculosis, both temperature and pulse are erratic and remain irregular after the spirochetes disappear from the sputum. In other words, relief from the spirochetosis does not appreciably simplify the picture.

In acute bronchospirochetosis, arsenicals, injected intravenously, give immediate relief. The fever drops, the pulse becomes regular and the respiration normal. This important improvement is obtained from the initial dose but ordinarily a second and, perhaps, a third administration are necessary for recovery. Bloedorn and Houghton used 0.6 gm. neo-arsphenamin as an initial dosage, followed by 0.5 gm. (?), and then by 0.9 gm., repeated at weekly intervals. The first three injections were apparently necessary for recovery, although immediate administration of the arsenical on admission to the hospital, instead of two weeks later, might have reduced the amount of treatment necessary. In the Chinese cases, in spite of the chronic nature of the infection, arsenicals are specific and relatively rapid in their spirocheticidal properties. Wylie gave an initial dose of 0.45 gm. and a second and third dose of 0.6 gm., each. A similar result was obtained for Wuchang Case 1, although the amount of neo-arsphenamin was slightly larger. The temperature drops almost immediately after each injection and is not followed by chills and sweats as when complicated by pulmonary tuberculosis. It remains nearly normal after the second dose, although the spirochetes do not usually disappear until some time later. Furthermore, there is usually a marked general improvement. The effect of this spirocheticide on the disease, even in an aggravated chronic stage, apparently meets Manson-Bahr's objection [6] that the causal relationship of *Spironema bronchiale* to the bronchial infection in which it is found has not been proved.

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6. Manson-Bahr, P. H.: Manson's Tropical Diseases, a Manual of the Diseases of Warm Climates, London, Cassell and Co., 1921, 960 pp.

In tuberculous infections (Wuchang, Cases 4 and 5) the administration of arsenicals eliminated spirochetes from the sputum but did not materially relieve the patient. Temperature and irregular pulse persisted, while no bodily improvement was noted.

The administration of potassium iodid, sodium cacodylate and other therapeutic agents has been found valuable in bronchospirochetosis, but per orem treatments do not have such specific properties as does the intravenous administration of arsenicals. Single doses of the latter alleviate, but, apparently, a cumulative effect is required for killing the spirochete.

A most interesting phase of the study of bronchospirochetosis is the blood picture. In all cases on record there is a reduction in red cells and a reduced hemoglobin percentage. The leukocytes may be either reduced, increased or normal. In one of Chalmers and O'Farrell's cases, an Arab, the red cells numbered 3,648,000 per c. mm. during the attack and 4,400,000 per c. mm. during the interval between attacks, with 80 per cent. hemoglobin during the attack and 100 per cent. in the interval. There was a marked leukopenia, 2,719 per c. mm., with eosinophils 2.6 per cent. of the total.

Nolf's case 2,[7] the only one of his histories with a complete leukocyte picture, showed a slight leukopenia (from 4,400 to 4,800), with 1 per cent. eosinophils.

The Chinese cases reviewed vary as to the red count, but all show a reduction in the number of cells and in the percentage of hemoglobin. One case shows a leukopenia (5,000), one case is only slightly above normal, while three cases show a leukocytosis. In each case the picture approaches normal with treatment. Of greater interest, however, is the grouping on the basis of the eosinophils. With tuberculous complication the eosinophil count, as observed, is less than 1 per cent. In the other three cases (simple infection) eosinophilia is extremely high (from 12 to 20 per cent.). This high percentage is reduced after treatment. It seems worth while, therefore, to inquire into the possible value of the eosinophil index as a means of ascertaining whether bronchospirochetosis, as determined by detection of the spirochete in the sputum, is a simple infection or constitutes part of a more complicated picture.

If one regards all varieties of spirochetes of the respiratory tract (exclusive of the mouth) as *Spironema bronchiale*, but capable of different manifestations, the organism must, then, be considered as highly adaptive. However, Nolf's organism [7] differs considerably from the typical agent of bronchospirochetosis both in structure and in the effect on the host. It seems probable, therefore, that it belongs to a

7. Nolf, P.: Fetid Spirillar Bronchitis and Pulmonary Gangrene, Arch. Int. Med. **25**:429 (April) 1920.

different group. There yet remain those types causing rhinitis, those with bronchial and lobar involvement and those with only bronchial infection. There is also the record of bronchial spirochetosis with pleural involvement (Mason[8]). It seems possible that careful examination will reveal all of these several types in China.

In cases that have been called to my attention, the spirochetes are more readily demonstrated in subacute cases than in chronic ones. Furthermore, there is some evidence to support the view that they can be recovered more easily from mucopurulent sputum several hours after an attack of hemoptysis than in the blood streaked sputum.

While the records from China cited here are incomplete and show the need of further observation, it is hoped that these preliminary data will serve as a stimulus to observation of the disease in other centers in China, and to more thorough study of both the clinical and laboratory evidence of the infection. Such study is especially important in view of the widespread incidence of pulmonary tuberculosis in China. Detection and treatment of simple infection with bronchial spirochetes will not only bring immediate relief to such cases but will reduce the amount of routine observation and diagnosis in suspected tuberculosis patients who do not react to tuberculin.

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8. Mason, V. R.: Pleural Spirochetosis, Johns Hopkins Hosp. Bull. **31**:435, 1920.

TETANY

A REPORT OF CASES WITH ACID-BASE DISTURBANCE *

SAMUEL B. GRANT, M.D.

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The symptoms of tetany occur in a number of widely differing conditions, such as disease of the stomach, overdosage with sodium bicarbonate, prolonged hyperpnea, absence of the parathyroid glands, and in infants as a clinical entity often associated with rickets. Recently there has been a considerable amount of research into the physiologic phenomena underlying the increased irritability of nervous and muscular tissues in these conditions, and various theories as to its etiology have been advanced. The chief of these are that it is due to a disturbance of the acid-base equilibrium in the body and to a disturbance of the calcium metabolism.[1]

Acid-base disturbance, consisting of an increase in the ratio of sodium bicarbonate to carbonic acid, is found in overdosage with sodium bicarbonate, in prolonged hyperpnea and in pyloric obstruction. The uniform hydrogen ion concentration of the body fluids is largely dependent on the maintenance of a constant $\frac{Na\ H\ CO_3}{H_2\ CO_3}$ ratio, according to the generally accepted view, and any marked increase in the ratio might be expected to result in a shifting of salt balance, and physiological disturbances in the body.

In overdosage with sodium bicarbonate ($NaHCO_3$) this agent is added to the blood faster than it is neutralized or excreted, hence the "alkali reserve" becomes greatly increased,[2] and there is presumably an increase in the ratio. In hyperpnea the carbonic acid in the blood is decreased by washing out of carbon dioxid faster than sodium bicarbonate is decreased by excretion or neutralization, and there is thus a relative excess of alkali, and an increase in the ratio.[3] In tetany with pyloric obstruction the explanation is held to be quite different. Hydrochloric acid, formed by the reaction $NaCl + H_2CO_3 = H\ Cl + Na\ H\ CO_3$, is secreted into the stomach, but in the presence of pyloric obstruction cannot pass through to the intestines to stimulate the alkaline intestinal secretion. There is, therefore, left in the blood

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Wilson, Stearns and Thurlow: J. Biol. Chem. **23**:89, 1915. Wilson, Stearns and Janney: J. Biol. Chem. **23**:123, 1915. McCann: J. Biol. Chem. **35**:553, 1918. MacCallum and Voegtlin: J. Exper. M. **11**:118, 1909. MacCallum and Vogel: J. Exper. M. **18**:618, 1913. Howland and Marriott: Quart. J. M. **2**:289, 1918. Kramer, Tisdall and Howland: Am. J. Dis. Child. **22**:431 (Nov.) 1921.

2. Harrop: Bull. Johns Hopkins Hosp. **30**:62, 1919.

3. Grant and Goldman: Am. J. Physiol. **52**:209, 1920.

an excess of sodium bicarbonate. This view is supported by the work of McCann,[1] who reported an increase in the plasma carbon dioxid capacity of animals in experimental tetany accompanying pyloric obstruction. MacCallum and his co-workers[4] have added the observation that blood chlorids are reduced, and Hastings, Murray and Murray[5] have found the blood sodium content also decreased. It seems not unlikely that the chlorid content is reduced by the secretion of hydrochloric acid into the stomach and loss by vomiting, and possibly sodium is decreased by excretion in an alkaline urine.

Calcium deficiency in the blood has repeatedly been found in parathyroid tetany[6] and in infantile tetany (Howland and Marriott;[1] Kramer, Tisdall and Howland[1]). The majority of investigations indicate that there is no "alkalosis" in these conditions. MacCallum[4] Tokuji and Togawa[7] and Hastings and Murray[6] were unable to find the increase of plasma carbon dioxid reported by McCann[1] in parathyroidectomized dogs. Wilson and his co-workers[1] concluded, from studies of the dissociation constant of hemoglobin, the alveolar carbon dioxid pressure, the hydrogen ion concentration of blood and urine, the ammonia content and total acidity of urine, that there is an "alkalosis" in parathyroid tetany. Greenwald[8] has recently advanced objections to the conclusions drawn from this work.

Noel Paton, Findlay and Watson[9] have found an increase in guanidin and methyl guanidin in the blood and urine in parathyroid and infantile tetany. They corroborate the observation of other investigators that administration of guanidin and methyl guanidin results in hyperexcitability very similar to that seen in tetany.

In a recent paper Freudenberg and Gyorgy[10] have attempted to correlate all forms of tetany as being due, in the final analysis, to calcium deficiency in the tissues. It is well recognized that such a deficiency leads to hyperexcitability in irritable tissues. Their theory is based, among other things, on the observations that calcium union with colloids may be influenced by changes in hydrogen ion concentration, by changes in calcium ion concentration, and by such substances as phosphate, acetate, nitrate and bicarbonate ions, and by protein derivatives with free amido groups, such as methyl and trimethylamin, guanidin, methyl guanidin, creatin, etc. They state, that in conditions in which there is an increase in the ratio of sodium bicarbonate to carbonic acid, free calcium ions in the blood decrease, being added to

4. MacCallum, et al.: Bull. Johns Hopkins Hosp. **31**:1, 1920.
5. Hastings, Murray and Murray: J. Biol. Chem. **46**:223, 1921.
6. Hastings and Murray: J. Biol. Chem. **46**:233, 1921.
7. Tokuji and Togawa: J. Lab. & Clin. M. **5**:299, 1919.
8. Greenwald: Proc. Soc. Exper. Biol. & M. **18**:228, 1921.
9. Paton, Findlay and Watson: Quart. J. Exper. Physiol. **10**:203, 1916.
10. Freudenberg and Gyorgy: Jahrb. f. Kinderh. **96**:5, 1921.

the total of calcium bound with colloids in the blood. As a result of this, the equilibrium between ionized blood calcium and calcium bound with tissue colloids is disturbed, calcium enters the blood stream from the tissues, and increased irritability occurs. The calcium content in the blood should, therefore, be increased, and, as a matter of fact, very slight increases in serum calcium have been reported in tetany of hyperpnea [3] and in tetany with experimental pyloric obstruction.[5] The occurrence of tetany without this acid-base disturbance they explain by the action of the protein derivative substances with free amido groups. These directly restrict calcium union with colloids, thus decreasing tissue calcuim, and causing increased irritability. Calcium enters the blood from the tissues, causing presumably an increased blood calcium content at the outset. But by calcium excretion the equilibrium between blood and tissue is reestablished, blood calcium being adjusted to the lower level of tissue calcium. In this process the percentage of diffusible calcium in the blood should not be altered, and Meysenbug and McCann [11] have found the same percentage of diffusible calcium in normal blood and in the calcium poor blood of dogs with parathyroid tetany.

This theory of Freudenberg and Gyorgy,[10] although very interesting, is by no means proved, and is not without objections. For instance, the carbon dioxid tension of serum was varied from 17 to 62 mm. by Meysenbug and his co-workers [12] without any detectable change in the percentage of diffusible calcium.

Luckhardt and Rosenblom [13] found that tetany could be prevented in parathyroidectomized dogs by injecting Ringer's solution intravenously two or three times daily. This procedure causes a marked diuresis, and presumably the elimination from the body of toxic substances such as guanidin. When the injections were stopped, symptoms of tetany developed. Of particular interest is the observation of these investigators that calcium free Ringer's solution produced the same effect as ordinary Ringer's solution, tetany being prevented when it was injected, occurring when the injections were stopped, and ceasing when they were started again. Thus, as the authors state, the production of diuresis is apparently more important than the administration of calcium in preventing tetany. However, it cannot be concluded from the fact that calcium free Ringer's solution prevented tetany, that there is no disutrbance of calcium balance in this condition. Any procedure causing marked diuresis would probably have the same effect.

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11. Meysenbug and McCann: J. Biol. Chem. **47**:541, 1921.
12. Meysenbug, Pappenheimer, Zucker and Murray: J. Biol. Chem. **47**:529, 1921.
13. Luckhardt and Rosenblom: Proc. Soc. Exper. Biol. & M. **19**:129 1921.

Six cases of tetany in adults, in which various interesting points are illustrated, have been studied at the Peter Bent Brigham Hospital. Four of these were observed by me, and two were taken from the case histories in the hospital records.

REPORT OF CASES

CASE 1.—*History.*—J. E. W. (Med. No. 17581), a clerk, aged 20, entered the hospital Jan. 13, 1922, with a history of intermittent epigastric distress, heartburn, gaseous eructation, nausea and vomiting extending over a period of two years. For three weeks prior to admission he had had severe stabbing and cramping pains in the epigastrium, copious vomiting and spasms of the hands and feet, the latter occurring almost daily for about a week. Because of these spasms there had been difficulty in handling small objects.

Examination.—The Roentgen ray showed a greatly dilated stomach and almost complete pyloric obstruction. Fractional gastric analysis disclosed marked hyperacidity, free hydrochloric acid in 10 c.c. of the fasting contents, and in three specimens removed at forty minute intervals after the test meal, titrating with 6.8, 8.5, 13 and 8 c.c. of decinormal sodium hydroxid, respectively.

ACID-BASE EQUILIBRIUM IN CASE 1

	Plasma CO_2 Capacity in Vol. %	Plasma Chlorid * Mg. NaCl per 100 C.c.	Whole Blood Chlorid Mg. NaCl per 100 C.c.	Serum Calcium † Mg. per 100 C.c.
January 18	98	...	...	....
January 19	86	...	...	....
January 20	87	524	250	12.4
January 21	83	...	...	....
January 23	60	...	...	....
January 25	72	...	...	....
January 26	63	600	...	14
January 31	59	571	480	....
February 13	60	600	436	12.5

* Method of Folin and Whitehorn.
† Method of Kramer and Tisdall.

Course.—With rest in bed and atropin, 0.0005 gm. by mouth, three times a day, and the same dose hypodermically on five occasions during attacks of pain, the vomiting rapidly decreased, and in a few days the pains occurred only once in twenty-four hours. On two occasions there were transient spasms of the hands, but unfortunately these occurred at about 2 a. m., and were not observed. There was a definite Chvostek sign of tetany, i. e., tapping the face over the seventh nerve caused a contraction of the muscles of the upper lip. Compressing the arm above the elbow resulted in tingling and numbness in the hands, and the fingers involuntarily became partially flexed, but no definite spasm occurred. On reference to the accompanying table it is seen that January 18 the plasma carbon dioxid capacity was found to be greatly elevated. January 20, the plasma chlorids, and especially the whole blood chlorids, were reduced, the latter to 50 per cent. of normal. After January 20 the epigastric pain and cramps ceased, and the patient did not vomit, except once January 22 and again January 25. The plasma carbon dioxid capacity and the plasma chlorids became normal by January 26. On this day, after the blood analysis had been done, a large duodenal ulcer was found at operation, and a gastro-enterostomy was performed. Convalescence was uneventful, and symptoms of tetany did not recur. The serum calcium content throughout was within the upper limits of normal. The fact that the whole blood chlorid was so markedly decreased, compared with the relatively small decrease of plasma chlorid, indicates that the blood cells must have been virtually free of chlorin.

CASE 2.—*History.*—G. B. B. (Med. No. 14040), a foundryman, aged 43, with a history of abdominal pain and frequent vomiting for thirteen years, and occasional attacks of "cramps" in the arms and legs for five years, entered the hospital July 22, 1920, with well developed signs of tetany. The forearms, hands and fingers were in continuous flexion.

Examination.—The roentgen ray showed a dilated stomach and almost complete pyloric obstruction. The plasma carbon dioxid capacity was 87.8 volume per cent.

Course.—Sodium chlorid was given per rectum, intravenously and by mouth, coincident with some improvement in the patient's condition, but without evidence of the causal relationship of this therapy to the improvement, the patient having recovered from his previous attacks spontaneously. The excretion of chlorid in the urine was greatly below normal, analysis of twenty-four hour urine specimens of the second to the fifth day in the hospital showing 0.50, 1.5, 0.81, and 1.8 gm., respectively. This may be accounted for, in part, by the small amount of food which the patient was retaining. Unfortunately, the chlorid content of the blood was not determined. The plasma carbon dioxid capacity remained greatly elevated. July 23, 24, 26, 27, 30 and August 2 it was 98, 96, 84, 77, 79 and 75.5 volume per cent., respectively. The patient's general condition improved, and the spasm relaxed, but did not disappear completely. Permission to operate for relief of pyloric obstruction was refused, and the patient was discharged against advice August 3, still having occasional attacks of vomiting, and spasm of the hands when at rest. One year later it was learned that the patient was dead.

CASE 3.—*History.*—J. W. (Med. No. 6164), a stage hand, aged 55, entered the hospital Feb. 19, 1917, with a history of epigastric distress and vomiting for three months, and rapid loss of weight. The day before death, after three days of very frequent vomiting, he was found to have typical spasms of tetany in the hands and forearms. One hour and fifteen minutes before death there was a "sort of convulsion," the patient stopped breathing for a short while, and then breathed irregularly until death.

Necropsy disclosed an annular constricting carcinoma at the junction of the duodenum and jejunum. The stomach, pylorus and duodenum were greatly dilated. Liver, gallbladder and bile ducts were normal. Unfortunately, no blood analysis was done on this patient. However, the case is interesting, inasmuch as the obstruction was at the end of the duodenum, allowing the secretion of the alkaline bile and pancreatic fluids to be stimulated by the gastric contents. Fractional gastric analysis had shown a normal amount of free and combined acid in the stomach contents. Apparently the secretion of acid was relatively greater than that of alkali.

CASE 4.—*History.*—F. L. (Med. No. 14833), a female clerk, aged 23, was admitted to the hospital Nov. 23, 1920, with gastric symptoms of three years' duration.

Examination.—The roentgen ray confirmed the diagnosis of gastric ulcer, and treatment by the Sippy method was started.

Course.—Because free acid persisted in portions of the gastric contents removed during the night, administration of alkali was rapidly increased, until the patient was receiving 10 gm. sodium bicarbonate every hour, and 1.2 gm. magnesium oxid and 3 gm. calcium carbonate at alternate hours, from 7:30 a. m. to 7:30 p. m. At the end of the fifth day of this medication she felt nauseated, vomited once, for the first time during treatment, and noticed a prickling sensation in the hands, and "stiffness" in the face. The mouth became somewhat puckered up, so that there was difficulty in speaking, and the eyelids were partially closed. Spasm developed in the hands, the fingers becoming partially flexed, and the patient was unable to open them to hold a drinking glass. This persisted for only a few minutes, and in about ten minutes the patient felt entirely normal. Administration of alkali was discontinued, and no further spontaneous spasm occurred. The following morning the plasma carbon dioxid capacity was 90.5 volume per cent. At this time there was a definite Trousseau sign of tetany, i. e., compressing the arm above the elbow resulted in

tingling and prickling sensations in the hand, gradual flexion of the fingers at the metacarpal phalangeal joints and adduction of thumb. The patient could not voluntarily overcome this spasm. There was also a faint Chvostek sign, tapping over the facial nerve caused slight twitching of the muscles about the mouth. These signs decreased somewhat, and Sippy treatment, with smaller doses of alkali, was again instituted. Three days after the appearance of tetany there were still signs of latent tetany, and the plasma carbon dioxid capacity was 91 volume per cent. Ten days later, when there were no signs of tetany, it was 71 volume per cent.

CASE 5.—*History.*—M. J. H. (Med. No. 16151), a housewife, aged 29, entered the hospital May 28, 1921, with toxemia of pregnancy, greatly reduced renal function, severe acidosis and frequent vomiting. Plasma carbon dioxid capacity was 19.5 volume per cent.

Course.—Because of this acidosis, 500 c.c. of 4 per cent. sodium bicarbonate solution was given intravenously and Murphy drip with 2 per cent. sodium bicarbonate was started, followed by a rise of carbon dioxid capacity to 27 volume per cent. The intravenous injection of sodium was repeated, vomiting decreased, and 2 gm. of sodium bicarbonate was given by mouth every two hours. Three days after admission to the hospital the plasma carbon dioxid capacity was 67.5 volume per cent. The following day the patient developed typical carpal spasm of tetany, the forearms were flexed and folded over the chest, the wrists were moderately flexed, and the fingers partially flexed at the metacarpal phalangeal joints and extended at the interphalangeal joints, and the thumbs were adducted. There were also occasional twitchings of the muscles about the mouth. Plasma carbon dioxid capacity at this time was 87 volume per cent. Administration of alkali was discontinued and spontaneous spasm soon disappeared, but a markedly positive Trousseau sign of tetany could be elicited from then until death five days later. The plasma carbon dioxid capacity remained above normal, and several hours before death was still 79.5 volume per cent.

CASE 6.—*History.*—E. M. (Med. No. 16492), a pupil nurse, aged 20, of neurotic temperament, became hysterical after failing to pass her examinations, and began to breathe very rapidly and deeply. She then complained of numbness and tingling in the fingers. After stopping the hyperpnea, the sensations disappeared. Later in the day the rapid deep breathing returned, tingling in the fingers started again, and the hands rather suddenly became spastic, the fingers and hands being flexed, and the phalanges extended. The arms soon became flexed at the elbows, and there was a sense of tightness in the abdominal muscles. She was persuaded to breathe quietly, and the spasm subsided in a few minutes. The following morning there was a mild recurrence of the hyperpnea, with tingling in the fingers, but no spontaneous spasm.

Examination.—Compressing the arms above the elbow for a few minutes resulted in a typical spasm of tetany in the hands. There was no Chvostek sign. She soon began to breathe quietly and all signs of tetany disappeared. The plasma carbon dioxid capacity during the attacks was not determined, but there is every reason to believe that it would have been low, due to the decrease of carbon dioxid in the blood accompanying overventilation. Grant and Goldman[9] found symptoms of tetany identical with those in this patient in voluntary forced respiration. Carbon dioxid is "washed" out of the blood, leaving a relative excess of sodium bicarbonate, and in the restablishment of the $\frac{NaH\ CO_3}{H_2\ CO_3}$ ratio, alkali passes out of the plasma into the tissues and into the urine, resulting in a reduced plasma carbon dioxid capacity.

SUMMARY

1. The occurrence of tetany in various disorders of the body is discussed. These disorders may be divided into two groups: (a) pyloric obstruction, hyperpnea and overdosage with sodium bicarbonate, which

have in common a disturbance of the acid-base equilibrium, due to an increase in the ratio of sodium bicarbonate to carbonic acid ($Na\,H\,CO_3 : H_2\,CO_3$) in the blood. (b) Infantile tetany and parathyroid tetany, in which there is a calcium deficiency in the blood. The theory of Freudenberg and Gyorgy, which attempts to explain all tetany as being due to a deficiency of calcium in the tissues, is discussed.

2. Six cases of tetany in adults are reported. These are all of the type in which there is an acid-base disturbance. Three cases occurred in obstruction of the stomach. In two of these the plasma carbon dioxid capacity was determined, and found greatly increased. In one the blood chlorid was determined and found markedly decreased. Serum calcium, determined in this case, was in the upper limits of normal. These results corroborate in the human the experimental findings of investigators in animals. Two cases resulted from overdosage with sodium bicarbonate, and one occurred in hysterical hyperpnea.[14]

14. After this paper was written Freudenberg and Gyorgy [Klinische Wchnschr. **1**:410, 1922] reported cases of infantile tetany in which the symptoms rapidly disappeared following ingestion of from 3 to 7 gm. ammonium chlorid per day. The use of this drug was suggested by the recent work of Haldane (J. Physiol. **55**:265, 1921), who found that the administration of large doses of ammonium chlorid by mouth caused an acidosis in the human, apparently by the formation of urea and hydrochloric acid. The symptomatic cure of infantile tetany by the drug is, therefore, strong evidence in favor of the view that there is an "alkalosis" in this condition.

THE BLOOD PRESSURE OF NORMAL CANTONESE STUDENTS

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It has been a common observation of my colleagues and myself that the blood pressure of Chinese patients in the Canton Hospital usually registered below the normal recognized for the peoples of Europe and North America. It was, therefore, decided to make a systematic study of the pressure of normal Cantonese young men with the idea of determining the average norm for that race.

Various methods have been employed by research workers in order to determine the blood pressure. Perhaps, the most accurate data are those obtained by the Erlanger sphygmomanometer. In reviewing the literature we find, however, that the mercury instruments are those most generally employed. The aneroid Tycos instrument is preferred by some.

METHODS OF READING

In the earlier reports, the systolic pressure was determined by palpation of the pulse. The diastolic and pulse pressures cannot be determined accurately by this method.

More recently as a result of the suggestion of Korotkoff,[1] the auscultatory method was introduced for reading the pressure. By this method it is universally recognized that the first sound or beginning of the first phase represents the systolic pressure. In regard to the diastolic reading, there has been considerable difference of opinion. Barach and Marks [2] in a series of observations on healthy students read the diastolic pressure in the fourth phase with some and with others at the disappearance of all sound, or the fifth phase. The difference in readings at these two points was generally about 5 mm. of mercury, but was as great as 10 mm. in some. Judson and Nicholson [3] recommend reading at the fourth phase. They claim that by reading at the fifth phase, there is an error of from 11 to 20 mm.

Murray [4] also agrees that the diastolic pressure must not be read below the fourth phase. Warfield,[5] however, states that the fifth phase may be used, and from the fourth to the fifth there is usually only from 4 to 6 mm. difference.

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1. Korotkoff: Tr. Imp. Acad. Med., St. Petersburg, **15**:365, 1905.
2. Barach, J. H., and Marks, W. L.: Arch. Int. Med. **13**:648 (May) 1914.
3. Judson, C. F., and Nicholson, P.: Am. J. Dis. Child. **8**:257 (Aug.) 1914.
4. Murray, J. R.: Brit. M. J. **1**:697, 1914.
5. Warfield, Louis M.: Am. J. M. Sc. **154**:414, 1917.

According to Weysse and Lutz,[6] "Fischer (1908), Lang and Manswetowa (1908), Van Westenrijk (1908) and Warfield (1912) consider the beginning of the fourth phase as the auscultatory index for minimum pressure; while Ettinger (1907), Gittings (1910) and Goodman and A. A. Howell (1910) consider the fifth phase as the correct index." They conclude that "Since the onset of the fourth phase is coincident with the marked decrease in amplitude of the oscillations recorded by the Erlanger sphygmomanometer, it should be considered as the index of minimum blood pressure."

Finally, MacKenzie,[7] quoting W. A. Jaquith, states that "The fourth point is shown to be more liable to incorrect estimation than the fifth," and he further adds that the fifth point thus appears to be the one at which, for the sake of uniformity and accuracy, we should ask an examiner to take the diastolic reading. In one set of readings the average difference between points four and five was only 6 mm. in 1,835 examinations.

In view of these conflicting opinions, we have generally advised those not very well accustomed to the use of the sphygmomanometer, to read the diastolic pressure at the disappearance of all sound. In the statistics given herewith, however, we have generally used the fourth phase for recording diastolic pressure, though, in some cases probably, the mercury was read between the fourth and fifth phases.

THE NORMAL PRESSURE

For comparative purposes, the first essential is the determination of a normal average in some particular race.

Systolic Pressure.—It has been asserted[8] that the normal systolic pressure for any age is roughly 100 mm. of mercury, plus a figure represented by the age in question. The difficulty with much of the data at hand is that it deals with special groups of individuals, as, for example, insured persons, athletes, army recruits, etc.

One of the most thorough of the earlier investigations was Woley's[9] study of 1,000 healthy persons ranging from 15 to 65 years of age. The palpatory method was used and for the whole series he obtained an average of 127.5 mm. for males and 120 mm. for females. For the period from 15 to 30 years of age, the average was 122 mm.

McCrae[10] states that for adults a systolic pressure of 110 or less may be called "low blood pressure." Fraser and Cowell[11] made a study of the pressure in normal soldiers and obtained an average of systolic from 110 to 120 mm.

6. Weysse, A. W., and Lutz, B. R.: Am. J. Physiol. **32**:427, 1913.
7. MacKenzie, L. F.: Med. Rec. **97**:1029, 1920.
8. Editorial: J. A. M. A. **75**:1650 (Dec. 11) 1920.
9. Woley, H. P.: J. A. M. A. **55**:121 (July 9) 1910.
10. McCrae, T.: M. Clin. N. America **3**:1177 (March) 1920.
11. Fraser, J., and Cowell, E. M.: J. A. M. A. **70**:520 (Feb. 23) 1918.

Barach and Marks [2] examined a group of healthy male students, mostly from 15 to 25 years of age. The systolic pressure varied from 90 to 200 mm., but the majority were between 110 and 140 mm. In more than 600 cases, 204 were recorded between 120 and 130 mm. of mercury. In 90 per cent. the systolic pressure was less than 150 mm.

Lee [12] examined Harvard freshmen. The average age was 18 years, the average height 5 feet 8 inches, and the average weight, stripped, 143 pounds. The average systolic pressure was 120 mm. and only 12.8 per cent. showed a systolic pressure above 140.

The Diastolic and Pulse Pressures.—The diastolic and pulse pressures were not recorded in the older studies and accurate data have only in recent years been obtained, especially since the introduction of the auscultatory method of reading. MacWilliam and Melvin,[13] in a series of healthy young adults, found the average diastolic pressure to be 65 mm. with a range from 50 to 80 mm. The average pulse pressure was 46 mm. Barach and Marks,[2] in their series, found that in 92 per cent., the diastolic pressure did not exceed 100 mm. and readings from 30 to 130 mm. were obtained. The great majority, however, ranged from 70 to 100 mm. The pulse pressure ranged from 20 to 70 mm. in 88 per cent. of their cases, a large proportion ranging from 30 to 60 mm. The extreme limits of pulse pressure were from 5 to 100 mm.

In Lee's study,[12] only five subjects had a diastolic pressure higher than 100 mm., the average being 80 mm.

Warfield [5] gives a normal variation for the pulse pressure of from 30 to 50 mm.

Fraser and Cowell,[11] in their series of soldiers, give from 70 to 80 mm. for the diastolic average and 40 mm. as the average pulse pressure.

Influence of Age on Blood Pressure.—In dealing with younger subjects age is such an important factor that disregard of it renders statistics valueless. Wolfensohn-Kriss [14] determined the systolic pressure of healthy children (Table 1), and concludes that the pressure increases with age, height and weight. In children of the same age, taller and heavier subjects gave higher pressure readings than shorter and lighter subjects. In boys and girls of the same weight, the pressure readings for boys were slightly higher than those for girls, but, in general, she concludes that there is practically no difference noted for boys and girls of the same heights and weights (Tables 4 and 5).

Fisher [15] gives the average systolic pressure for accepted insurance risks at from 15 to 39 years (Table 1).

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12. Lee, R. I.: Boston M. & S. J. **173**:541, 1915.
13. MacWilliam, J. A., and Melvin, G. S.: Brit. M. J. **1**:693, 1914.
14. Wolfensohn-Kriss, P.: Arch. f. Kinderh. **53**:332, 1910.
15. Fisher, J. W.: Proc. Assn. Life Ins. Med. Directors N. America, 393, 1912.

TABLE 1.—The Systolic Blood Pressure According to Age of Different Races by Various Observers

Age	Wolfensohn-Kriss[14]	Fisher[15]	Katzenberger Several Observers[16]	Judson and Nicholson[3]	Faught[18]	Alvarez[19]	Hunter[21]	Willits	Faber and James[22]	McCay[23] Bengali	Musgrave and Sison[29] Filipinos	Chamberlain[30] White Men in Philippines	Chamberlain[30] Filipinos	Concepción and Bulatao[31] Filipinos	Trimble, Chinese	Whyte, Chinese	Cadbury, Cantonese
6	...	...	95	93.8	80-100	...	...	...	94.5	.....	.....	.....	.....	.....	...	...	...
7	90	...	103	87.9	.....	...	...	...	97.3	.....	.....	....	.....	.....	...	...	65
8	...	...	99	93	.....	...	...	...	99.2	.....	.....	.....	.....	.....	...	...	80
9	90	...	97	91.7	90-105	...	...	...	100.9	.....	.....	.....	.....	.....	...	...	84
10	...	...	104	99	.....	...	...	...	102.4	.....	.....	.....	.....	.....	...	...	80
11	98	...	107	95.8	.....	...	...	...	104.1	.....	.....	.....	.....	.....	...	...	83
12	...	..	108	90.9	95-110	...	...	...	105.9	.....	.....	.....	.....	.....	...	...	88
13	99	...	114	104	.....	...	...	...	107.6	.....	.....	.....	.....	.....	...	...	89
14	...	...	..	105.8	.....	...	...	...	110.0	.....	.....	.....	.....	.....	...	...	97
15	101	...	...	99.6	95-115	...	...	...	112.2	.....	.....	.....	.....	.....	..	99	97
16	...	...	...	....	.....	126	...	...	115.3	.....	.....	.....	.....	.....	...	104	100
17	113	118	...	....	95-120	128	120	...	.....	.....	.....	.....	.....	.....	...	104	100
18	...	...	...	....	.....	127	...	120	.....	.....	.....	.....	112.8	110.7	...	108	102
19	...	...	...	....	.....	126	...	...	.....	.....	.....	115	.....	.....	97	116	105
20	...	...	...	....	.....	126	...	...	.....	.....	.....	.....	.....	.....	...	111	103
21	...	...	...	....	.....	125	...	...	.....	.....	.....	.....	.....	.....	..	113	102
22	...	123.5	...	....	.....	126	122	...	.....	90-105	.....	.....	115.4	.....	...	122	108
23	...	...	..	....	.....	126		123	.....	.....	.....	.....	.....	.....	...	...	93
24	...	...	...	....	.....	130	...	...	....	.....	.....	.....	.....	.....	...	130*	103
25	...	...	...	....	.....	126	...	...	.....	.....	.....	.....	.....	111.9	90	130*	100
26	...	..	...	...	.....	...	...	...	.....	.....	.....	.....	.....	.....	...	...	95*
27	...	125.6	...	..	.....	...	123	...	.....	.....	.....	115.9	117	.....	...	...	110*
28	...	...	...	....	.....	126	...	124	.....	.....	.....	.....	.....	.....	...	...	...
29	...	...	...	....	.....	...	...	...	.....	.....	108	.....	.....	.....	...	...	95*
30	...	...	...	....	.....	...	...	...	.....	.....	.....	.....	.....	.....	...	...	105*
31	...	...	...	....	.....	...	...	...	.....	.....	.....	.....	.....	.....	...	...	130*
32	...	125.5	...	....	.....	126	124	124	.....	.....	.....	116.7	116.9	118.8	101		
33	...	...	...	....	.....	...	...	...	.....	.....	.....	.....	.....	.....			
34	...	...	...	....	.....	...	...	...	.....	.....	.....	.....	.....	.....			

* Only one case for this age was reported.

Katzenberger [16] gives the general average systolic pressures of eight other observers and her own (Table 1) for different ages.

According to Judson and Nicholson,[3] in a study of 1,344 children, the widest variations occur from the tenth to the fourteenth year. The systolic pressure shows a gradual rise from the third to the tenth year and from 10 to 14 there is a more abrupt rise. The systolic pressure varies from 91 mm. in the fourth year to 105.5 mm. in the fourteenth year. There is no arithmetic increase from year to year, from 4 to 14 there being only a total rise of 14 mm.

TABLE 2.—Diastolic Pressure by Age

Age	Judson and Nicholson[3]	Faber and James[22]	Concepción and Bulatao,[21] Filipinos	Trimble, Chinese	Whyte, Chinese	Cadbury, Chinese
6	62.5	64				
7	64.2	65.4	....	..	..	35
8	50.6	66 7	....	..	..	50
9	62.2	67.8	....	..	..	53
10	64.6	68.9	....	..	..	51
11	62.3	69.9	....	..	..	50
12	50.6	71.1	....	..	..	55
13	63.2	71.9	....	..	..	56
14	63.7	73.3	....	..	..	50
15	61.8	74 6	....	..	63	60
16	....	75.8	....	..	70	60
17	....	....	....	..	70	63
18	....	....	77.6	..	68	64
19	....	....	....	55	77	65
20	....	....	....	..	74	62
21	....	....	....	..	72	63
22	....	....	....	..	78	59
23	....	....	....	..	..	59
24	....	....	....	..	76*	57
25	....	....	76.6	56	72*	73
26	....	....	....	..	..	70*
27	....	....	....	..	..	85*
28	....	....	....			
29	....	....	....	..	..	70*
30	....	....	....	..	..	75*
31-40	....	....	80.3	62	..	80* and 50*

* One case only.

There is little increase of the diastolic pressure, so that the pulse pressure increases more in proportion than the systolic pressure.

Observations were made by the pith ball oscillation method, a modified Erlanger apparatus and the ordinary mercury sphygmomanometer, using auscultation for reading the pressure. The observations by these methods differed slightly. In Tables 2 and 3 are recorded only the results obtained by auscultation.

Bing [17] examined 138 men, all inmates of an institutional "home," and found that the systolic pressure ranged from 115 to 145 mm. He states that the normal systolic blood pressure seems to be from 100 to 130 mm.

16. Katzenberger, A.: Ztschr. f. Kinder. **9**:167, 1913.
17. Bing, H. I.: Ugesk. f. Laeger, **77**:923, 1915; abstr. J. A. M. A. **65**:468 (July 31) 1915.

Faught's [18] averages for systolic pressure cover the ages 6 to 17 years (Table 1).

A very careful analysis of the systolic blood pressure readings of all freshmen entering the University of California has been contributed by Alvarez.[19] The readings for 2,930 males were taken with the men lying down. The curve of average pressure does not rise steadily, but drops between ages 17 and 21. The upper normal limit for men he places at 130 mm. Fifty per cent. of the readings were between 116.5 and 136.5 (Table 1).

TABLE 3.—PULSE PRESSURE BY AGE

Age	Judson and Nicholson[3]	Faber and James[22]	Concepción and Bulatao,[21] Filipinos	Trimble, Chinese	Whyte, Chinese	Cadbury, Chinese
6	30.3	31.1				
7	22.7	32	....	..	..	30
8	33.4	33.1	....	..	..	28
9	29.5	33.8	....	..	..	31
10	34.4	33.9	....	..	..	29
11	33.5	34.6	....	..	..	33
12	40.3	35.2	....	..	..	33
13	30.8	36.1	....	..	..	33
14	42.1	37.5	....	..	..	35
15	37.7	38.5	....	..	[illegible]	36
16	....	39.6	....	..	..	41
17	....	....	....	..	[illegible]	37
18	....	....	33.1	..	[illegible]	39
19	....	....	....	40	[illegible]	40
20	....	....	....	..	37	41
21	....	....	....	..	42	40
22	....	....	....	..	44	42
23	....	....	....	..	..	34
24	....	....	....	..	54*	40
25	....	....	....	..	58*	27
26	.. .	....	35.3	34	..	25*
27	....	....	....	..	..	25*
28	....	....	.. .			
29	....	....	....	..	..	25*
30	.. .	....	....	..	..	30*
31-40	....	....	38.5	39	..	50* and 40*

* One case only.

According to Hunter and Rogers,[20] men over weight average a higher systolic pressure than men under weight. A variation of 15 mm. below the average or 15 mm. above is within normal limits.

One of the most extensive series of studies of the systolic pressure is that given by Hunter [21] on 67,000 life insurance cases (Table 1).

MacKenzie [7] states that the systolic pressure increases with increased weight, disregarding age and height. The latter has little effect. There is little change in the pulse pressure until after 40 years of age.

For the period of from 15 to 29 years, the average systolic pressure is 122 mm., the diastolic 85 mm. and pulse pressure 43 mm. From

18. Faught, F. A.: Blood Pressure from the Clinical Standpoint, Ed. 2. W. B. Saunders Company, Philadelphia, 1916.
19. Alvarez, W. C.: Arch. Int. Med. **26**:381 (Sept.) 1920.
20. Hunter, A., and Rogers, O. H.: Proc. Assn. Life Ins. Med. Directors N. America **6**:92, 1919.
21. Hunter, A.: Proc. Assn. Life Ins. Med. Directors N. America **7**:153, 1920.

30 to 44 years of age, the systolic pressure is 125 mm., diastolic, 88 mm., and pulse pressure 43 mm. Any diastolic pressure at any age, under 60 mm. or over 103 mm. is abnormal if constant.

Pulse pressures over 60 mm. or under 25 mm. are cause for close scrutiny of every other feature.

According to a leaflet signed by Dr. Charles H. Willits, medical director of the Provident Life and Trust Company, Philadelphia, and issued to medical examiners, accepted risks between ages 15 and 60 years should have an average systolic blood pressure between 120 and 135 mm. (Table 1). A normal diastolic pressure may be between 60 and 105 mm.

Faber and James [22] studied the pressure in 651 boys and 450 girls aged from 3 to 17. The subjects were normal, mostly school children. They state that age is as satisfactory as any factor, such as height or weight, in determining the normal pressure. In order to smooth out the curves, three ages were grouped together. Thus for age 6, the averages for 5, 6 and 7 were added together and divided by 3. In Tables 1, 2 and 3 we record the readings for the boys only.

Other Factors Causing a Normal Variation in Blood Pressure.—It is well known that many factors cause a normal variation in blood pressure. Thus Katzenberger [10] in a series of observations noted that the blood pressure tends to fall as the rate of the pulse increases. The lower blood pressure in young children is to be explained by the undeveloped condition of the heart and blood vessels. As height and weight increase, the systolic pressure increases also. Therefore the pressure of children living under good conditions is higher than in children placed in bad conditions. Boys have higher pressure due to their greater size. Sleep causes a fall in pressure. Position, psychic phenomena, time of day, taking food or fluid, movements of the body, respiration and bathing all affect the pressure.

Faught [18] observed that with puberty, adult pressure is established. There is a fall of pressure with increased altitude. In persons of neurotic temperament, according to Goodman,[23] the blood pressure is likely to be elevated.

Lowered pressure is said [24] to be the result of a weakened heart, as in convalescence from disease, and also as the result of a lack of dynamic force in the individual.

Fraser and Cowell [11] noted that in soldiers actually engaged in fighting, especially infantrymen, the average systolic pressure worked out higher than among men in the same regiment in support, where they were only exposed to occasional fire. The increased pressure of the

22. Faber, H. K., and James, C. A.: Am. J. Dis. Child. **22**:7 (July) 1921.
23. Goodman, E. H.: Blood Pressure in Medicine and Surgery, Lea & Febiger, Philadelphia, 1914, p. 64.
24. Moulton, R. H.: The Forecast, p. 171 (Sept.) 1921.

fighting man tended to drop quickly when he was resting away from the firing line, so that a systolic pressure of 140 mm. might fall to 110 or even to 100 mm.

The influence of age has been already referred to and Norris [25] states that preceding the onset of puberty, there is a tendency toward a fall of pressure; during pubescence there is a period of increased pressure which is, in turn, followed by a slight decrease after puberty has been established.

The rate of the pulse is thought by Woley [9] to be a factor. In cases with a pulse under 65, he found the pressure to average 123, while, if the pulse was over 85, the pressure reached 130 mm.

TABLE 4.—Systolic Pressure According to Height

Height in Centimeters	Wolfensohn-Kriss[14]	Michael[20]	Chamberlain,[30] White Men in Tropics	Cadbury, Chinese
90-100	85	99	.....	70
101-110	89	109	.. ..	65
111-120	90		.....	82
121-130	93	112	.....	84
131-140	95	118	.....	87
141-150	101	120	.....	90
151-160	104	125	117.9*	100
161-170	110		114.7 116 115.5 116.2	102
171-180	...	...	115.7 116.2 117.9	105
181-190	...	...	119.3 120.6	105

* Under 162.5 cm.

The effects of height and weight have already been referred to. These factors have been especially considered by Michael.[20] She studied 128 normal children and found that there was a regular rise in systolic pressure with an increase in height and weight. This is also confirmed by the work of Wolfensohn-Kriss [14] and Chamberlain [30] (Tables 4 and 5).

The effects of climate are referred to by Castellani and Chalmers [27] as lowering the tension of the pulse, with dilatation of peripheral vessels and increased elasticity of the pulse.

25. Norris, G. W.: Blood Pressure, Lea & Febiger, 1917, p. 378.
26. Michael, May: Am. J. Dis. Child. **1**:272 (March) 1911.
27 Castellani & Chalmers: Manual of Tropical Medicine, Ballière, Tindall & Cox, London, 1919, p. 75.

Variations in Blood Pressure by Race.—We come now to the question of racial variations. But little mention has been found of variations because of race in the textbooks on blood pressure, and we have been able to find only a few references in literature.

McCay [28] studied the blood pressure of more than 500 adult male Bengalis, aged from 20 to 25 years. They were Hindus from Lower Bengal. The Riva-Rocci instrument was used with a broad armlet. The systolic pressure only was determined, by palpation, with the patient sitting. The average pressure was found according to one report to be from 83 to 118 mm. of mercury, but, in the later report, he states it was from 90 to 105 mm. or generally just under 100 mm.

To explain this low pressure, McCay considers climatic conditions are not the chief cause, because Europeans living in Calcutta did not show this low pressure, they averaging from 115 to 130 mm. of mercury. As the capacity for muscular work in Europeans is superior, we may

TABLE 5.—Systolic Pressure According to Weight

Weight in Kg.	Wolfensohn-Kriss[14]	Michael[26]	Cadbury, Chinese
16-20	82	95	81
21-25	92	100	83
26-30	94	107	87
31-35	95	112	94
36-40	99	116	96
41-45	108	122	100
46-50	111	126	101
51-55	112	...	104
56-60	...	...	106
61-65	...	...	106

assume that they also have superior muscular power in both voluntary and involuntary groups.

The Filipino has been studied more carefully with regard to his blood pressure than other Oriental races. The first work was done by Musgrave and Sison.[29] The study was made on ninety-seven Americans and Europeans and forty Filipinos, mostly students. The ages varied from 25 to 40 years. They concluded that the systolic pressure of persons living in the tropics is lower than the general averages given. The heart and blood vessels are not to blame. Variation in the volume and viscosity of the blood may be a factor. Anemia is not a cause. The most probable cause is the lowered peripheral resistance that occurs in the tropics.[27] If this be true, then the lowered blood pressure may be explained in two ways: the secretory function of the skin is increased

28. McCay, David: Lancet **1**:1483, 1907; Scientific Memoirs, Govt. of India, No. 34, p. 23, 1908.

29. Musgrave, W. E., and Sison, A. G.: Philippine J. Sc. B. **5**:325, 1910.

and probably the normal surface resistance and vasomotor tension necessary to produce the required surface heat of temperate climates is greatly diminished in the tropics, the year round.

There are also to be considered the splanchnic influences which control vasomotor tone.

For foreigners, the following pressure readings were obtained:

Duration of Residence in Tropics	Systolic Pressure
1 month to 1 year	124 mm.
1 year to 5 years	115 mm.
5 years to 10 years	116 mm.
Over 10 years	113 mm.

Of the Filipinos, thirty males gave an average systolic pressure of 108 mm. and nineteen females of 113 mm.

A very extensive study was carried out by Chamberlain.[30] He studied the systolic pressure of 1,042 healthy, white, American soldiers, aged mostly from 20 to 40 years, and 386 Filipinos representing various tribes, and including soldiers, laborers, servants and convicts. Most of these were under 42 years of age. Chamberlain assumes a normal of from 115 to 150 mm. of mercury for men from 15 to 30 years of age, living in the temperate zone.

In the Philippines, he finds the average pressure for white men at this age to be 115 and from 30 to 40 years of age to be 118 mm. Seasonal changes and complexion—blond or brunet—did not affect the systolic pressure. He suggests that there is a vasoconstriction of superficial blood vessels.

For Filipinos between 15 and 40 years, Chamberlain found an average systolic pressure of from 115 to 116 mm. He concludes that there is no essential difference from white men in the blood pressure (Table 1).

A later study of Filipinos has been made by Concepción and Bulatao,[31] using an Erlanger sphygmomanometer. Readings were obtained from 697 males and 218 females, varying in age from 15 to 87 years. The males were chiefly convicts and medical students. The females were also convicts and students. The results may be found in Tables 1, 2 and 3. For the average age of males of 29.5 years and of females of 25.1 years, the average readings were as follows:

	Males	Females
Systolic Pressure	115.6 mm.	116 mm.
Diastolic Pressure	79.1 mm.	83.4 mm.
Pulse Pressure	36.4 mm.	32.6 mm.

There is to be noted a general tendency for the systolic, diastolic and pulse pressures to ascend with age. They conclude that, "The

30. Chamberlain, W. P.: Philippine J. Sc. B. **6**:467, 1911.
31. Concepción, I., and Bulatao, E.: Philippine J. Sc. B. **11**:135, 1916.

systolic pressures of Filipinos are very much lower than those of Americans living in temperate climates (Woley), but the same as those of Americans living in the tropics (Chamberlain)."

In sixty-five opium habitués the blood pressure was much below the average of other cases.

Investigations of American Indians were carried on by Harley Stamp [32] including tribes living in the arctic as well as the temperate zone. He concludes that "the normal age charts of blood pressure records on the American Indian differ but slightly from those of the white man, except that there seems to be a uniform tendency to reduced blood pressure at or about 45 years."

Blood pressure in the Japanese has been studied by Tanemura [33] who examined 2,842 healthy male and 1,100 female Japanese. The ages varied from 4 to 25 years. He used a von Recklinghausen tonometer, reading by Korotkoff's auscultatory method. The results were recorded in centimeters of water. The average height for boys of 4 was 93 cm., for boys of 19, 160.3 cm. The body weight was 13.6 kg. for boys of 4 and 54.1 kg. for men of 21. The annual increase in the blood pressure was particularly marked in boys from the thirteenth to the seventeenth years. In general, the curve of rising blood pressure ran parallel with those of body height and weight.

The normal pressure at 4 years of age for boys was systolic, 72 mm.; diastolic, 49 mm. of mercury (98 and 67 cm. water). It rose gradually to systolic 122 mm.; diastolic 83 mm. of mercury (165 and 112 cm. water) in men of 19.

The pulse pressure rose from 23 mm. of mercury (31 cm. water) at 4 years to 40 mm. of mercury (54.5 cm. water) in men of 19.

BLOOD PRESSURE IN CHINESE

Beyond the records of Chinese here collected, I know of no statistics on this race in the literature.

A questionnaire was sent out to missionary physicians throughout China and answers giving records of normal persons were received from only three: Drs. C. G. Trimble, Duncan Whyte and H. W. Boyd. Doctor Trimble sent in records for thirty-two normal male Chinese. Twenty-four were from the province of Fukien, which lies between 23 and 29 degrees north latitude, and eight from other provinces of China. The occupations of the Fukinese varied from that of student, merchant, druggist, coolie, soldier, barber, shoemaker, baker, boat man, preacher and farmer. The Pilling special sphygmomanometer was

32. Faught, F. A.: l. c., 18, p. 161.
33. Tanemura, I.: Kyoto J. M. Sc. **15**:84, 1918; Abstr. China M. J. **34**:542, 1920.

used with the auscultatory method. The ages varied from 18 to 43 years and the average pressures obtained were as follows: Systolic: 100; diastolic, 61; pulse, 38 (Tables 1, 2 and 3).

The eight subjects from other provinces of China varied in age from 19 to 28 years. Four were from the province of Chihli, two from Shantung, one from Kiangsu and one from Hunan, all in Central or North China. The average pressures were as follows:

Systolic	106 mm.
Diastolic	66 mm.
Pulse	40 mm.

Dr. G. Duncan Whyte's studies were made on healthy students in Swatow, which is located in the northern part of Kwangtung Province. He employed the Faught instrument and the auscultatory method. There were eighty-five males varying in weight from 25.8 to 64.4 kg. (57 to 142 pounds) and in height from 137 to 176 cm. (54 to 69½ inches). The ages varied from 15 to 25 years. There were only two subjects over 22 years of age. For the other eighty-three men he obtained the following averages:

Systolic	109 mm.
Diastolic	71 mm.
Pulse	38 mm.

For the pressures recorded for each age, see Tables 1, 2 and 3.

Dr. H. W. Boyd, of Canton, studied fifteen men and ten women from the provinces of Kwangtung and Kwangsi. Their ages ranged from 18 to 54 years, averaging 28 years, and their occupations were those of farmer, mechanic, merchant, student, housewife, prostitute, nurse, druggist, soldier, physician and laboratory assistant. Their weights varied from 26.3 to 66.2 kg. (58 to 146 pounds) and their heights from 139.7 to 182.8 cm. Doctor Boyd used a Tycos instrument with the auscultatory method. He obtained the following averages:

Systolic Pressure	107 mm.
Diastolic Pressure	67 mm.
Pulse Pressure	40 mm.
Average Pulse Rate	81 mm.

My investigation of the blood pressure of healthy Cantonese was conducted as part of a general program of determining the characteristics of normal Chinese.

The records were all obtained from healthy Chinese students of the two southern provinces of China known as Kwangtung and Kwangsi. Canton, the capital of Kwangtung, lies on latitude 23 degrees 06.'1 north and the two provinces lie between 20 and 26 degrees north latitude.

It is well known that the Cantonese differ in many ways from the people of other parts of China. They are shorter, lighter and with smaller features. Unlike most people living in the tropics, they are noted for their energy and progressiveness.

All of my records were taken in the routine physical examination of 774 students of the Canton Christian College. These young men live in much better hygienic conditions than the average Chinese. They take part in athletic sports and eat a better quality of food. Their life is very similar to that of American boys.

All students with cardiac murmurs or other evidence of cardiac or pulmonary disease were excluded. My records are based therefore on the examinations of only healthy young men.

A Nicholson sphygmomanometer was used, employing the auscultatory method. A 14 cm. wide cuff was used on the right arm, with the subject sitting and resting his arm on a table.

The systolic reading was made at the first appearance of sound and the diastolic at the fourth phase, but, in the younger boys, the diastolic reading was often very indefinite. Taking the averages for certain age periods, we find as follows:

7 to 14 years	Systolic	83 mm.
	Diastolic	51 mm.
	Pulse	31 mm.
15 to 20 years	Systolic	101 mm.
	Diastolic	62 mm.
	Pulse	39 mm.
21 to 30 years	Systolic	101 mm.
	Diastolic	68 mm.
	Pulse	36 mm.

By reference to Tables 1, 2, 3 and 6 the detailed figures may be observed.

There is very probably a slight error in the age factor in a few of the cases, since Chinese generally estimate their age as one year older because they count that they are one year old at birth. However, even by the most casual glance at the figures in Table 1, it is clearly evident that the Cantonese youth has normally a systolic pressure considerably lower than that found in Europeans and Americans. It follows closely Musgrave's figures for Filipinos, but is lower than that reported by Chamberlain and Concepción and Bulatao. It is also lower than the records for Japanese, but compares with what was found among Bengali.

Diastolic pressure is also lower than what has been recorded by other observers, but the pulse pressure is slightly higher than found in one of the studies of Filipinos.

Objection is taken sometimes to the misleading character of averages. We have, therefore, taken the systolic readings for ages 15 and 20 and

grouped them in their order of frequency. The average readings were 97 and 103, respectively. The percentages for different readings were as follows:

	Age 15	Age 20
71 to 80 mm. Hg	12%	4%
81 to 90 mm. Hg	31%	13%
91 to 100 mm. Hg	19%	38%
101 to 110 mm. Hg	31%	22%
111 to 120 mm. Hg	6%	16%
121 to 130 mm. Hg	1%	7%

Thus 81 per cent. of the readings for age 15 were between 81 and 110 mm. For age 20, 60 per cent. of the readings were between 91 and 110 mm.

TABLE 6.—Blood Pressure of Healthy Male Chinese Students of the Canton Christian College

Age	No.	Average Pressure			Systolic Pressure		Diastolic Pressure		Pulse Pressure		Average Rate of Pulse
		Systolic	Diastolic	Pulse	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	
7	2	65	35	30	70	60	40	30	30	30	78
8	11	80	50	28	95	60	60	35	40	20	89
9	18	84	53	31	100	60	75	35	50	15	92
10	28	80	51	29	110	60	70	35	50	15	90
11	31	83	50	33	100	65	75	30	45	10	86
12	48	88	55	33	115	65	75	20	60	15	84
13	47	89	56	33	105	75	70	40	50	15	85
14	63	97	59	35	125	75	85	30	65	15	84
15	90	97	60	36	130	75	80	35	70	15	82
16	101	100	60	41	130	70	85	35	70	10	83
17	97	100	62	37	130	75	90	40	70	10	83
18	81	102	64	39	130	75	85	45	70	10	82
19	65	105	65	40	130	70	80	45	65	10	81
20	46	103	62	41	125	85	80	50	65	20	78
21	18	102	63	40	125	85	80	50	65	20	80
22	13	108	59	42	155	85	80	45	65	20	81
23	5	98	59	34	110	80	65	53	57	15	78
24	2	103	57	40	105	100	60	55	40	40	60
25	2	100	73	27	100	100	80	65	35	20	77
26	1	95	70	25	...	..	..	..	..	..	72
27	1	110	85	25	...	..	..	..	..	..	64
29	1	95	70	25	...	..	..	..	..	..	88
30	1	105	75	30	...	..	..	..	..	..	72
31	1	130	80	50	...	..	..	..	..	..	81
36	1	90	50	40	...	..	..	..	..	..	72

Following Wolfensohn-Kriss and Michael, I have estimated the blood pressure in accordance with weight (Tables 5 and 7). Here the age factor was not involved, except that all measurements were made in male subjects from 7 to 36 years of age.

The systolic pressure shows an increase from 81 mm. in boys weighing from 16 to 20 kg. to 106 mm. in young men of 61 to 65 kg. weight or an increase of 25 mm. The diastolic pressure shows an increase of 15 mm. and the pulse pressure a much less marked increase.

Wolfensohn-Kriss' figures closely parallel my own up to the 40 to 45 kg. limit. After that, her records are higher. Michael, on the other hand, gives considerably higher reading throughout the series.

If height is taken as the standard for estimating the pressure, there is also found to be a progressive increase as the subject grows (Tables 4 and 8).

Thus between the 101 to 110 cm. group and the 171 to 180 cm. group, the systolic pressure rises 40 mm., the diastolic 25 mm. and the pulse pressure 16 mm.

Comparing my readings with those of other observers, the Cantonese shows a marked inferiority in blood pressure taken with reference to his height.

TABLE 7.—AVERAGE BLOOD PRESSURE OF CANTONESE MALES ACCORDING TO THEIR WEIGHT

Weight in Kg.	Number	Average Systolic	Average Diastolic	Average Pulse
11–15	1	60	30	30
16–20	30	81	51	29
21–25	66	83	51	32
26–30	85	87	55	32
31–35	70	94	60	34
36–40	67	96	59	37
41–45	141	100	60	40
46–50	160	101	63	32
51–55	107	104	64	40
56–60	35	106	65	41
61–65	9	106	66	41

TABLE 8.—AVERAGE BLOOD PRESSURE OF CANTONESE MALES ACCORDING TO THEIR HEIGHT

Height in Cm.	Number	Average Systolic	Average Diastolic	Average Pulse
90–100	1	70	40	30
101–110	3	65	41	23
111–120	27	82	50	31
121–130	68	84	52	32
131–140	89	87	55	32
141–150	93	96	59	37
151–160	200	100	61	39
161–170	256	102	63	39
171–180	32	105	66	39
181–190	1	105	70	35

DISCUSSION

It thus appears that the systolic blood pressure of Cantonese and other Chinese young men from the South of China averages from 20 to 30 mm. of mercury less than the normal for people in Europe and North America. Correspondingly low systolic pressure has been observed among Bengali and Filipinos.

The diastolic pressure of the Chinese is also lower than the generally accepted normal, but by only 10 to 20 mm. The Filipinos' diastolic pressure seems to be higher.

The average pulse pressure shows little variation from the generally accepted normal, and is, therefore, relatively high.

In our studies there is a regular arithmetic increase of systolic and diastolic pressure values from 7 to 22 years of age. A less regular increase is observed in the pulse pressure.

In this connection it is a remarkable fact that hypertension as a pathological condition in Chinese is very unusual. In an extensive medical practice of more than twelve years in Canton, I have rarely met with hypertension, either with or without signs of nephritis, although chronic Bright's disease is very common. When met with, marked hypertension has generally been associated with aortic valvular disease of the heart. Other observers in Canton have confirmed my findings.

In looking for a possible explanation, the following suggestions have come to me: (1) Use of opium; (2) decreased capacity for muscular effort, causing a decrease in muscle tone; (3) small stature and lighter weight; (4) deficient suprarenal or other hormones in the body, producing a lack of dynamic force; (5) the large vegetable diet. A Chinese subsists chiefly on rice, with only minute amounts of meat. (6) Simplicity of life, and absence of nervous strain; (7) effects of the tropical climate causing (a) constant dilatation of the peripheral blood vessels; (b) the secretory function of the skin is increased and probably the normal surface resistance and vasomotor tension necessary to produce the required surface heat of temperate climates is greatly diminished in the tropics the year round; (c) splanchnic influences. The vasomotor tone of the splanchnic system has a marked effect on motor tone; (d) a vasoconstriction of the superficial blood vessels; (e) variations in the volume and viscosity of the blood.

In my studies of the Cantonese youth, I can exclude Numbers 1 and 2 as possible factors. Number 3 is applicable, as my studies prove that the Cantonese is shorter in stature and of lighter weight than American and European youth. Number 4 is at present based on theory, but I have seen no lack of vigor or dynamic force in our students.

It may be inferred that diet and the various factors listed under climate have a bearing on the phenomena.

CONCLUSION

A study of the blood pressure of 774 healthy, male, Cantonese youths shows that their average systolic, diastolic and, to a less degree, pulse pressures, are lower than the standards for European and American youth of corresponding age, weight or height.

RENAL FUNCTION AND THE AMOUNT OF FUNCTIONING TISSUE

THE RATIO: $\frac{\text{UREA IN ONE HOUR'S URINE}}{\text{UREA IN 100 C.C. OF BLOOD}}$ AFTER GIVING UREA AND WATER *

T. ADDIS, M.D.

SAN FRANCISCO

This is the first of a short series of papers, the outcome of an attempt to draw quantitative structural deductions from functional results. The few methods used are discussed and criticized only in reference to the question as to whether the results give information in regard to the amount of secreting tissue in the kidney. This narrow point of view has been adopted because the purpose of the inquiry is entirely utilitarian and clinical. All manifestations of renal function have an intrinsic interest from the standpoint of physiology, but it is maintained that only those from which we can draw quantitative conclusions about the amount of tissue in the kidney are of immediate and practical clinical importance.

Such an idea is foreign to nearly all the recent work on this subject. Nevertheless, from the time of Bright up to about the beginning of the last decade, the hope that functional methods might ultimately be used as a measure of the extent of a renal lesion was probably the main incentive to clinical investigation into the function of the kidney. But since Schlayer's papers were published, that is to say, during the very time when technical methods were so perfected as greatly to facilitate the mechanical side of the work, this hope appears to have been abandoned. Schlayer is largely responsible for this modern attitude of disillusion. He demonstrated that there was no quantitative relation between the function of the kidney, as he determined it, and the amount of damage it had suffered experimentally or through disease. But while he rejected the idea of drawing quantitative structural inferences from functional work, he believed that functional methods were of value in detecting, if not the amount, at least the location of disease in the kidney. He thought he could determine whether disease affected mainly the vessels or mainly the tubules. However, it was soon shown that it was impossible to make such a distinction by functional methods. This failure to draw even qualitative anatomic deductions from functional results had a marked psychologic effect; all the more, because, at the same time, the limitations of histologic methods were emphasized. Instances were cited in which no evidence of renal damage was obtained by microscopic examination, although there had been obvious indications of a failure of renal function, and, on the other hand, cases were

* From the Department of Medicine of Stanford University Medical School.

reported with apparently normal function in which gross manifestations of structural derangement were found. In view of all these facts ,the tendency of clinical investigators has certainly been to give up what seemed to be a hopeless attempt, to take what they did have—the functional results—and to try to establish classification and treatment on a functional rather than on an anatomic basis.

This view will not be held permanently. At best it is only a confession of failure, the result of inadequacies in present day functional and histologic methods. It can serve only as a preparation for a renewed attempt on the problem of the relation between renal function and structure, the problem which Bright set before himself nearly a century ago.

Improvement in functional methods has been mainly technical. We can now measure more easily, and also more accurately, the amounts of various substances eliminated by the kidney. But in other respects there has been little change. In particular, a fundamental principle applicable to all functional methods, when they are to be used for structural deductions, has been neglected almost entirely. Unless the functional manifestation is the maximal effort of which the organ to be tested is capable, no structural inferences can be drawn from it. For instance, it might be possible, from a measurement of the force exerted, to make a fairly accurate prediction as to the amount of muscular tissue concerned in some action, such as weight lifting—but only if the effort put forth were the greatest the muscles could perform. Thus, two different amounts of muscle tissue might both raise a 10 pound weight. No deduction as to their relative size could be made. But if it were to be found that in one case 50 pounds was all that could be lifted, while in the other case 100 pounds was the maximum, it would be legitimate to conclude, other things being equal, that one was twice as large as the other. In the kidney also the functional output must be at a maximum if quantitative deductions in regard to the amount of the secreting tissue are to be drawn.

In the above example the deduction as to the amount of muscular tissue from the functional result would be valid only if the conditions were such that extramuscular factors were equally operative. So, also, if renal function is to be used as a measure of the amount of secreting tissue, the extrarenal circulatory and nervous factors concerned in excretion must be uniform.

THE UREA RATIO TEST

The Ratio: $\frac{\text{Urea in one hour's urine}}{\text{Urea in 100 C.c. of blood}}$ after giving urea and water.

The development and some of the theoretic aspects of this test were dealt with in 1917.[1] Since then the technic has been modified as a

1. Addis: J. Urol. **1**:263, 1917.

result of further work on animals [2] and on man.[3] In its present form the method has been in use for two years in clinical work on Bright's disease, and it seems unlikely that any further considerable change will be required, although much remains to be done in regard to the establishment of standards of normality. Only the practical application of the test will be dealt with in this paper.

Two essential conditions are required. One is that the kidney should be placed under circumstances which call for great activity in urea excretion. The other is that there should be an absence of certain specific renal stimulants and depressants. The first is met by the administration of an amount of urea which will raise the concentration of urea in the blood reaching the kidney, while at the same time a diuresis is induced by water drinking. The second is fulfilled if the test is carried out in the morning, before the subject has taken food, and if the collections of urine and blood are not commenced until three hours after the urea has been taken.

The details of the procedure used in clinical work are as follows: At 6 a. m. the patient slowly drinks about 1,000 c.c. water in which urea is dissolved. When the blood urea concentration is between 15 and 25 mg. per hundred c.c., 30 gm. urea are given. If the blood concentration is already as high as 60 mg. of urea per hundred c.c., no urea need be taken. At intermediate blood urea levels appropriate quantities of urea are administered, so that when the first blood is collected it should have a concentration of between 60 and 90 mg. of urea per hundred c.c. At 7 a. m., and every hour thereafter until 11 a. m., the patient drinks two glasses of water. No breakfast is given. Urine is voided every hour, but at 9 a. m., the time at which urination is completed is noted to within thirty seconds, and at 10 a. m., 11 a. m. and 12 noon urine is passed directly into special bottles and the exact time noted. The patient must be instructed to make each voiding as complete as possible, and to take the time at the end, and not at the beginning of urination. For women a special commode is used with a large funnel emptying into a removable bottle. Blood is obtained at the middle of each of the three hourly periods over which urine is collected. The urea content of these urine and blood specimens must be estimated with a high degree of accuracy, for even small errors may markedly influence the ratio if they happen to be in opposite directions for the blood and for the urine.

When these conditions are observed the rate of urea excretion is governed by only two factors, the concentration of urea in the blood

2. Addis, Barnett and Shevky: Am. J. Physiol. **46**:1, 22, 39, 52, 1918. Addis, Shevky and Bevier: Am. J. Physiol. **46**:11, 129, 1918. Addis, Foster and Barnett: Am. J. Physiol. **46**:84, 1918.

3. Addis and Drury: Proc. Soc. Exper. Biol. & Med. **23**:24, 1920.

and the amount of secreting tissue in the kidney. Since the concentration of urea in the blood is determined, it follows that the ratio: $\frac{\text{rate of urea excretion}}{\text{urea in 100 c.c. of blood}}$, or as we measure it, $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$, is a measure of the amount of secreting tissue in the kidney.

When the amount of secreting tissue in the kidney is constant, the rate of urea excretion varies directly with the blood urea concentration. In the same normal adult individual the amount of renal tissue may be assumed to remain nearly constant, and if this statement is true, there should be a direct proportion between the amounts of urea in an hour's urine and the amounts of urea in 100 c.c. of blood, so

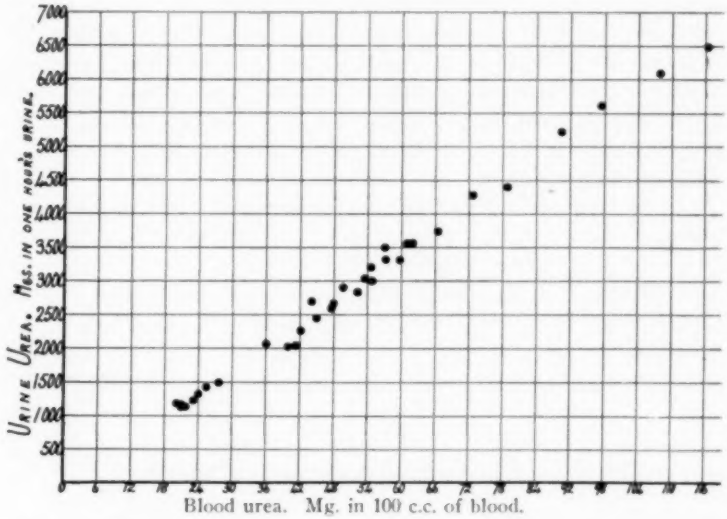

Fig. 1.—The amount of urea in one hour's urine is directly proportional to the amount of urea in 100 c.c. of blood, when the amount of renal tissue is constant, and when certain conditions are observed. Observations on the same subject at different levels of blood urea concentration.

that the rates plotted against their respective blood urea concentrations should fall in a straight line. Figure 1 shows a series of hourly rates measured in the same individual. The blood urea concentrations were varied by administering varying quantities of urea.

These experiments show that when the amount of renal tissue is constant there is a direct relation between the rate of urea excretion and the blood urea concentration, so that changes in the level of urea concentration in the blood between 20 and 120 mg. are associated with corresponding changes in the rate of urea excretion.

It should be emphasized that this is not a general law. It holds true only under the special and peculiar conditions which have been

outlined. We have many rates, observed in the subject from whom the measurements shown in Figure 1 were obtained, which show how far the rate of urea excretion may vary from any direct relation with the blood urea concentration, and we have already given many instances of great variations in the rate in spite of a constant blood urea concentration.[4] These variations are of particular interest and importance as showing the high degree of adaptability inherent in the mode of action of the kidney, and its freedom from subjection to merely physical and mechanical conditions. But when we wish to deduce the size of the kidney from its function, all this complex mechanism of adjustment, of concurrent or alternating inhibition and excitation, must be merged in the drive toward the maximum rate of excretion allowable under the circumstances. The fact that such a direct relationship between blood concentration and rate of excretion can be demonstrated, is an indication that we have succeeded in attaining this unity of action, and that under these special conditions all the circulatory and nervous factors concerned in renal activity are working together towards one end.

When the amount of renal tissue varies, the ratio: $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$ is directly proportional to the amount of secreting tissue in the kidney. This again, of course, is no general law, but is true only under the specific conditions described. The detailed proof will require much further work, but there is already sufficient evidence that it is at least approximately true. It has already been shown, though at that time the conditions under which the ratio ought to be measured were only imperfectly understood, that the loss of renal substance involved in the removal of one kidney,[5] or the variable loss arising from differing degrees of uranium intoxication,[6] was revealed by the degree of depression in the ratio. We are now engaged in a study of the relation between the weight of the kidneys and the magnitude of the ratio in rabbits. It appears that in the rabbit every 10 gm. of renal tissue—the average weight of both kidneys in a medium sized animal—will yield a ratio of approximately 1.75. In man the average weight of both kidneys is about 300 gm. If there is a direct relation between the magnitude of the ratio and the size of the kidney, we should, accordingly, expect to find that the average ratio in man was 1.75×30, or 52.5. Our present average for normal adults is 50.4—a sufficiently close agreement.

In Table 1 all the ratios obtained from normal persons under these conditions are given. There are 163 in all. The number of persons is

4. Addis and Watanabe: J. Biol. Chem. **27**:249, 1916.
5. Addis and Watanabe: J. Biol. Chem. **28**:251, 1916.
6. Watanabe, Oliver, and Addis: J. Exper. M. **28**:359, 1918.

thirty-one. Almost all of them were medical students between 23 and 30 years of age. In a few cases the amount of urea taken varied, but in the great majority 30 gm. were given. The average ratio is 50.4, the standard deviation ± 6.61 and the variability (the standard deviation as a percentage of the average) 13.1 per cent.

Part of the variability in the ratios obtained from different normal persons is no doubt due to differences in the amount of renal tissue

TABLE 1.—RATIOS OBTAINED FROM NORMAL ADULTS AFTER ADMINISTRATION OF UREA AND WATER

Name	Ratio	Name	Ratio	Name	Ratio	Name	Ratio
Dru.	56.9	Add.	45.1	Geo.	43.5	Nak.	43.0
	58.8		45.4		42.0		48.0
	56.0		42.3		38.5		47.0
	58.4		44.0		39.7		45.0
	57.6		51.4				
	54.4		42.9	Jac.	60.8	Ank.	48.4
	53.0		45.6		60.8		48.8
	54.6		44.8		61.4		50.0
	57.7		43.5		54.9		
	58.5		50.9			War.	45.9
	54.2		49.6	New.	39.2		49.1
	54.0		43.3		39.2		51.0
	53.6		41.9		39.8		
	49.1		50.9		39.6	Dia.	48.2
	50.4		47.8		38.3		45.5
	57.4		43.1		35.9		48.0
	55.3		45.3		38.5		
	53.4		49.3			Ves.	46.7
	56.1		44.3	Pis.	45.1		43.8
	55.0		50 7		58.7		53.8
	52.6		42.4		42.5		
	51.2				51.4	Dun.	50.5
	55.2	Jen.	54.1		55.3		48.5
	53.8		48.3		47.1		41 9
	58.4		51.1				
	57.4		46.6	Kol.	60.7	Moo.	50.0
	61.4				61.7		49 0
	58.5	Hun.	58.4		57.6		46.1
	55.4		58.2		58.2		
	56.4				56.9	Bin.	49 0
	57.6	Aze.	55.9		54.2		52.3
	59.0		52.6		56.0		47.7
	61.1						
		Har.	38.6	Col.	66.5	Sea.	54.5
Col.	41.2		38.1		59.4		55.1
	45.6		36.7		65.9		55.9
	44.2						
	47.4	Chr.	43.7			Kel.	51.5
			48.6	Cim.	52.4		51.6
Swe.	45.9				47.8		
	49.6	Pro.	46.3		44.8		
	45.8		54.0			Pie.	51.1
			54.4				47.0
Sel.	44.7			Mye.	46.0		46.2
	49.7				48.0		
	50.2	Nor.	53.2		48.5		
	55.6		56.9		39.5	Nap.	53.0
	54.5		58.6		41.0		55.6
	56.1		64.8		40.0		54.6

50.4.

they possess. The true variability, i. e., the fluctuations due to the influence of other physiologic factors then the size of the kidney and to errors in collection and chemical technic, can be gaged in a rough way from the variability of the ratio in a single person. We have thirty-three ratios in the subject Dru. and the variability is only 5.1 per cent., as compared with 13.1 per cent. in the group. Some means should be found whereby the effect of these variations in the amount

of renal tissue in normal persons could be discounted. It is highly desirable for adults, and in dealing with children it is absolutely necessary, for their ratios are, of course, much lower than those obtained from adults, so that no direct comparison is possible. There is no doubt some relation between body weight and renal weight, and in the case of children we correct the ratio by reference to a curve drawn from average figures given by Vierordt [7] on the percentage of kidney weight to body weight at different ages. But we have not found any data from which the reliability of this correction can be calculated.

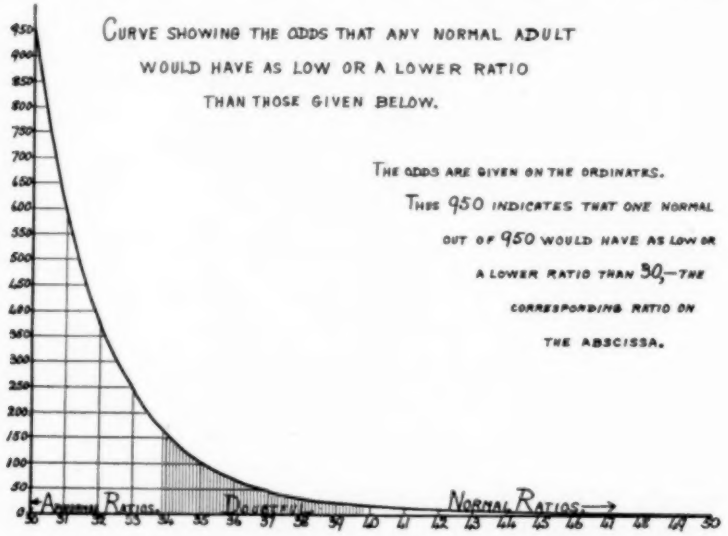

Fig. 2.—Provisional separation of ratio obtained in adult men or women into those which can be regarded as within the limits of normal variation (normal ratios), those which are regarded as beyond these limits (abnormal ratios), and those which cannot with any certainty be described as either normal or abnormal (doubtful ratios).

It seems likely that the relationship is far from being a close one. Warthin,[8] who has been interested in this subject, thinks that the most reliable estimate of the range of variation in renal weight in adults is from 110 to 145 gm. for the right kidney, and from 150 to 180 gm. for the left, and he is impressed with the variability of the relation between kidney weight and body weight. Stewart [9] recently published some figures which showed that kidney weight varied more

7. Vierordt: Arch. f. Anat. u. Physiol. Anat. Abt., Suppl. **62**: 1890.
8. Warthin, Practical Pathology, Ed. 2, George Wahr. Ann Arbor, Mich., p. 155.
9. Stewart, Am. Physiol. **57**:45, 1921.

directly with body surface than with body weight. We are at present collecting data on this question. In the meantime, it seems preferable to use the ratio without attempting any correction for adults even though the range in which there is doubt as to whether normality or abnormality exists is thereby considerably widened. From the average and standard deviation of the ratios obtained from normal persons we have calculated the odds that any normal person would have as low or a lower ratio than those given in Table 2. The limits of the normal, the doubtful and the abnormal are provisionally and arbitrarily indicated. They are also shown in Figure 2.

Examples of the application of this method in clinical work will be given in a later paper of this series. We have found it of value in the diagnosis, prognosis and treatment of Bright's disease.

TABLE 2.—THE ODDS THAT ANY NORMAL PERSON WILL HAVE AS LOW OR A LOWER RATIO THAN THOSE GIVEN IN THE TABLE

Ratio	Odds	
50.4 or less	1 in 2	Normal
40.5 or less	1 in 15	
39.8 or less	1 in 18	Doubtful
39.2	1 in 22	
38.5	1 in 28	
37.9	1 in 35	
37.2	1 in 44	
36.5	1 in 56	
35.9	1 in 72	
35.2	1 in 93	
34.5	1 in 122	
33.9 or less	1 in 162	Abnormal
33.2	1 in 213	
32.6	1 in 286	
31.9	1 in 385	
31.2	1 in 527	
30.6	1 in 741	
27.9	1 in 1,630	

CONCLUSIONS

1. Under certain special conditions, when the amount of secreting tissue in the kidney is constant, the amount of urea excreted in the urine in one hour is directly proportional to the amount of urea in 100 c.c. of blood sampled during that period.

2. Under certain special conditions, when the amount of secreting tissue in the kidney varies, the ratio: $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$ is directly proportional to the amount of secreting tissue in the kidney.

3. The conditions under which the ratio: $\frac{\text{urea in one hour's urine}}{\text{urea in 100 c.c. of blood}}$ becomes a measure of the amount of secreting tissue in the kidney are, first, that the urea excreting capacity be placed under a strain so that all the secreting tissue is called to full activity, and second, that there be an absence of the effect of certain specific renal stimulants and depressants.

STUDIES IN THE KOTTMANN REACTION FOR THYROID ACTIVITY*

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The function of the thyroid gland has been studied with, perhaps, greater interest and certainly with more profit by physiologists and clinicians than that of any other gland of internal secretion. During recent years in particular, a remarkable revival of clinical interest has become manifest, stimulated, no doubt, by a number of contributory factors, among which may be mentioned the isolation of thyroxin; the development of a number of simple instruments for the determination of basal metabolism; the study of coagulation alterations associated with thyroid dysfunction; the use of iodids and iodin in public health work, and the development of irradiation in the treatment of hyperthyroidism. It may, therefore, be warranted to present in some detail the study of the Kottmann reaction for thyroid activity, concerning which we have already published a brief note.[1]

Technic.—The technic of the reaction is simple and depends on the protective property of the serum for silver iodid. When the protective power is great, the size of the silver iodid particles dispersed in the serum remains small and the photosensitivity of the silver iodid is reduced. If the protective power of the serum is poor, the silver iodid forms larger particles, becomes more photosensitive, and will, on exposure to light and subsequent development, be readily reduced to metallic silver.

To 1 c.c. of clear serum, obtained preferably in the morning before meals, 0.25 c.c. of 0.5 per cent. solution of potassium iodid is added and 0.3 c.c. of a 0.5 per cent. solution of silver nitrate. The reagents should be prepared freshly and accurately measured. After mixing by gently agitating the tube, the serum is exposed for five minutes at a distance of 25 cm. to a 500 Watt mazda lamp. Then 0.5 c.c. of a 0.25 per cent. solution of hydrochinon is added, and the color changes noted at definite time intervals. Readings can be made on a 4 plus basis, or colorimetrically against some arbitrary color standard. In some of our work we have used a solution of dialyzed iron for this purpose and readings are then expressed in terms of a color unit. Serum from cases of hyperthyroidism retards the development of the brown color; normal serum turns brown within a short period of time; serum from cases of hypothyroidism accelerates the appearance of the dark brown color.

CLINICAL RESULTS

In our preliminary note we presented the results of 400 tests with this reaction, in which we found that in seventy cases of clinically

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1. Petersen, Dobler, Levinson and Laibe: J. A. M. A. **78**:1022 (April 8) 1922.

evident hyperthyroidism sixty-five serums markedly retarded the reaction, two retarded the reaction only slightly, two were normal and one serum accelerated the reaction. In forty-nine cases of simple goiter (colloid and adenomatous) the reaction was in all cases either within normal limits or the serum accelerated the reaction. In 139 serums from normal individuals, three retarded the reaction slightly.

Kottmann [2] found that the administration of bromids retarded the reaction, just as the addition of bromids directly to the serum retards

TABLE 1.—EFFECT OF ADDITION OF POTASSIUM IODID TO SERUM

Patient	Date	Medication	Diagnosis	Goiter	General Condition	Kottmann Reaction
W. H. K.	1/17/22	None	Syphilis	None	Good	+++
	1/19/22	KI (fasting serum)	.....	.....	.....	++
	1/23/22	KI (serum taken after meal)	.....	.....	.....	0
	1/26/22	KI	.....	.....	.....	++

TABLE 2.—EFFECT OF FRIGHT ON REACTION

Patient	Date	Diagnosis	Goiter	General Condition	Kottmann Reaction
H. D.	11/18/21	Minor gunshot wound of face 11/17/21	None	Extreme fright	0
	11/20/21	.....	.....	Nervous	+
N. S.	12/23/21	Automobile accident	None	Very nervous	0
	12/25/21	.....	.....	Still slightly nervous	+

TABLE 3.—EFFECT OF TRAUMA ON SERUM REACTION

Patient	Date	Diagnosis	Goiter	General Condition	Kottmann Reaction
L. S.	12/22/21	Contusion of brain	None	Drowsy	++
Johnson	11/17/21	Fractured humerus (Accident, 11/16/21)	None	Calm	++
H. S.	12/23/21	Contusion of brain (Automobile accident, 12/22/21)	None	Unconscious	++
	12/25/21	.....	.....	Unconscious	++
	12/26/21	.....	.....	Semiconscious	++

the reaction. We have studied this effect in a number of patients and have found it quite constant. Merke [3] has also confirmed this effect in the serum of epileptics when on bromid medication.

Inasmuch as an excess of iodid added to the serum retards the reaction, we have observed the effect of the administration of iodids in patients. Table 1 illustrates the change in the reaction.

It will be noted that the reaction is retarded, but not, as a rule, so completely as after the ingestion of bromids.

2. Kottmann, K.: Schweizer med. Wchnschr. **1**:644, 1920.
3. Merke, F.: Schweizer med. Wchnschr. **51**:200, 1921.

Fright.—We have observed a decided retardation of the reaction with fright, illustrated in Table 2.

On the other hand, in patients who had been injured, but were not frightened, or injured and unconscious, the serum reaction was found to be unaltered (Table 3).

The Effect of Thyroidectomy in Exophthalmic Cases.—In three cases thyroidectomy was carried out on patients with obvious symptoms of hyperthyroidism and the serum was examined before and after the operation (Table 4).

Effect of Irradiation.—We have had the opportunity of studying only one case in which the thyroid region was irradiated. The patient, Mrs. T., entered the Augustana Hospital with a history of nervousness. The thyroid gland was slightly enlarged, but there was no evidence of hyperthyroidism and the Kottmann reaction being normal, she was not subjected to operation. She was given one (two-third erythema dose) roentgen-ray treatment over the thyroid and thymic region, and the

TABLE 4.—EFFECT OF THYROIDECTOMY ON SERUM REACTION

Patient	Date		General Condition	Kottmann Reaction
H. K.	11/ 4/21	Before operation.....	Highly nervous	0
	11/18/21	Two weeks after operation.....	Still nervous	++
	12/ 2/21	.....	Still somewhat nervous	0
	12/ 9/21	.....	Still somewhat nervous	+
Miss B. S. ...	11/ 7/21	Before operation.....	Very nervous	0
	11/18/21	.....	Improved	+++
Mrs. A. J. K.	11/26/21	Before operation.....	Moderate symptoms	0
	1/11/22	.....	Improved	+
	1/14/22	.....	Improved	+++

Kottmann reaction made two weeks later before the patient left the hospital was completely retarded. There were, however, no evidences of hyperthyroidism even at this time.

EXPERIMENTAL DATA

In order to clear up a number of points observed with these clinical cases, we have carried out a series of animal experiments.

The Injection of Thyroxin.—We first studied the effect of thyroxin when injected into the blood stream, using dogs for this purpose.

EXPERIMENT 1.—Dog 210; weight 9,400 gm.; received 5 mg. thyroxin intravenously Nov. 28, 1921. Serum samples were taken as follows:

		Kottmann Reaction	
Sample 1:	Before injection	++++	(Dark brown)
" 2:	30 minutes after injection...	++++	(Dark brown)
" 3:	1 day after injection.....	++++	(Dark brown)
" 4:	2 days after injection.....	++++	(Dark brown)
" 5:	3 days after injection.....	+	(Faint brown)
" 6:	4 days after injection.....	—	(Unchanged)
" 7:	5 days after injection.....	—	(Unchanged)
" 8:	7 days after injection.....	+	(Died from distempter)

The fact that the effect of the thyroxin is not immediate, but that a latent period of several days elapses before the effect becomes apparent is illustrated in the second experiment as well as in the first.

EXPERIMENT 2.—Dog 220; weight 10 kg.; injected intravenously with 8 mg. thyroxin Dec. 12, 1921, at 11:30 a. m. Serum samples were taken as follows:

		Kottmann Reaction
Sample 1:	Before injection	++
" 2:	3 hours after injection	++++
" 3:	1 day after injection	++++
" 4:	3 days after injection	++++
" 5:	5 days after injection	+
" 6:	7 days after injection	—
" 7:	9 days after injection	+
" 8:	11 days after injection	+
" 9:	15 days after injection	+
" 10:	18 days after injection	++
" 11:	23 days after injection	+++

In this experiment the effect was first observed on the fifth day after injection and was still apparent after two weeks.

Thyroidectomy.—If injection of thyroxin is followed by a serum alteration made manifest in the Kottmann reaction by a lessening of the sensitivity to light, we might assume that extirpation of the thyroid would result in a hastening of the reaction. Kottmann has found this reaction to be accelerated in the serum obtained from myxedema patients.

In this group of animals a complete thyroparathyroidectomy was carried out, but in the relatively short period of time that the animals lived, there was no distinct evidence of an alteration of the reaction in the direction expected.

EXPERIMENT 3.—Dog 225; operated on Dec. 15, 1921; both lobes of thyroid removed.

		(Colorimeter Readings) Kottmann Reaction
Sample 1:	Serum before operation	1.7
" 2:	24 hours after operation	1.9
" 3:	2 days after operation	1.4
" 4:	4 days after operation	1.2
" 5:	6 days after operation	2.
" 6:	8 days after operation	1. (Distempter)
" 7:	12 days after operation	1.
" 8:	15 days after operation	1.
" 9:	19 days after operation	1.5

EXPERIMENT 4.—Dog 236; operated on Dec. 29, 1921; both lobes of thyroid removed.

Sample 1:	Serum before operation	2.0
" 2:	During anesthesia	2.2
" 3:	After 24 hours	1.5
" 4:	After 4 days	2.0

These experiments are, of course, not comparable to the effects that have been recorded by Kottmann with serum from hypothyroid cases. In these he found a well defined acceleration of the reaction as con-

trasted with the retardation found in hyperthyroidism. It is possible that if the animals were observed for a considerable time some alteration in the serum in the direction expected might be observed.

Massage of Thyroid Gland.—We next studied the effect of massage of the thyroid gland in dogs with goiters. It is, of course, known that the dogs of the Great Lakes region frequently have goiters. For our purpose we selected animals having a palpable enlargement.

EXPERIMENT 5.—Dog 243: Gland massaged Jan. 9, 1922.

		Kottmann Reaction
Sample 1:	Blood taken at 11:45 a. m.	2.4
" 2:	Masage of thyroid for 1 hour immediately after (12:45)	2.4
" 3:	Three hours after massage (3:45)	1.25
" 4:	24 hours later	1.0
" 5:	72 hours later	Colorless

EXPERIMENT 6.—Dog 245; Jan. 20, 1922.

		Kottmann Reaction
Sample 1:	At noon	2.2
	(Massage for two hours: 1:40 to 3:40 p. m.)	
" 2:	At 4 p. m.	2.2
" 3:	At 8:30 p. m.	2.2
" 4:	One day later, 1/21/22	2.2
" 5:	Three days later, 1/23/22	1.0
" 6:	Four days later, 1/24/22	0.0
	(Massage for one hour, 1/25/22)	
" 7:	Six days later, 1/26/22	0.0
	(Massage for one hour, 1/27/22)	
" 8:	Eight days later, 1:28/22	0.0
" 9:	Ten days later, 1/30/22	0.0

EXPERIMENT 7.—Dog 246; Jan. 24, 1922.

Sample 1:	At 10 a. m.	2.5
	(Massage two hours: 10 to 12 noon)	
" 2:	At 2 p. m.	2.2
" 3:	At 6 p. m.	2.2
" 4:	One day later, 1/25/22	1.6
	(Massage one hour, 1/27/22)	
" 5:	Four days later, 1/28/22	Colorless
" 6:	Six days later, 1/30/22	Colorless

The next dog used had no apparent goiter, but the thyroid gland could be palpated. The gland was massaged for one hour Jan. 27, 1922, and for one hour January 2. After the first massage the tissues of the neck were somewhat edematous and particularly the thyroid lobes were sensitive to touch. This continued for several days.

EXPERIMENT 8.—Dog 256; Jan. 27, 1922.

		Kottmann Reaction
Sample 1:	10 a. m., before massage	2.2
	(10 to 11, massage)	
" 2:	At 12 a. m.	2.2
" 3:	8 a. m., one day later, 1/28/22	2.0
" 4:	8 a. m., three days later, 1/30/22	2.0
" 5:	8 a. m., six days later, 2/2/22	0.4
	(Massage one hour)	
" 6:	Seven days later, 2/3/22	0.0

Irradiation.—The roentgen ray and other related physical agents have dual effects on tissues,[4] small doses causing stimulation (functional, formative, etc.) while large doses may cause functional paralysis and destruction of the cells. Like other glandular tissues the thyroid gland is relatively sensitive to irradiation. We might expect, therefore, that small doses would cause some stimulation of the gland and result in an alteration of the Kottmann reaction. We have carried out four experiments in this connection.

EXPERIMENT 9.—Dog 178; Oct. 29, 1921; irradiation over thyroid area at 8:45 a. m. (Dose: 5 minutes, Coolidge tube without filter; 5 inch spark, 10 inch focal distance; 3 ma.)

		Kottmann Reaction
Sample 1:	Serum before irradiation	0.0 *
" 2:	Serum 30 minutes after irradiation	0.9
" 3:	1 hour and 30 minutes after irradiation	0.18
" 4:	3 hours and 30 minutes after irradiation	0.33

In this experiment, extending over a short period of time, it becomes evident that the first effect of the irradiation is not one indicating hyperthyroidism.

EXPERIMENT 10.—Dog 179; Oct. 31, 1921. Irradiation as before.

		Kottmann Reaction
Sample 1:	Serum before irradiation	1.0
" 2:	30 minutes after irradiation	1.5
" 3:	1 hour and 30 minutes after irradiation	4.0
" 4:	5 hours after irradiation	0.0
" 5:	24 hours after irradiation	0.0

EXPERIMENT 11.—Dog 180; Nov. 1, 1921. Irradiation as before.

		Kottmann Reaction
Sample 1:	Serum before irradiation	1.3
" 2:	30 minutes after irradiation	2.5
" 3:	1 hour and 30 minutes after irradiation	1.1
" 4:	6 hours after irradiation	0.7

EXPERIMENT 12.—Dog 183; Nov. 1, 1921. Irradiation as before.

		Kottmann Reaction
Sample 1:	Serum before irradiation	1.0
" 2:	30 minutes after irradiation	2.2
" 3:	1 hour and 30 minutes after irradiation	2.2
" 4:	3 hours and 30 minutes after irradiation	2.2
" 5:	7 hours and 30 minutes after irradiation	1.1
" 6:	1 day after irradiation	0.5
" 7:	3 days after irradiation	0.0
" 8:	6 days after irradiation	0.0

All four experiments indicate that the first effect of the irradiation seems to increase the photosensitiveness of the reagents, the color developing more rapidly and to a greater depth in the serum samples taken during the hours immediately following the irradiation. After this time, however, the reaction is reversed and the serum reaction is retarded. In no case is the reaction retarded to the extent that one finds in serum from cases of hyperthyroidism.

* The reaction delayed, an experience met with not infrequently in dogs.

4. Petersen and Saelhof: Am. J. M. Sc. **163**:391 (March) 1922.

In the next dog the dose was increased (10 minutes) and the serum examined for a longer time after the irradiation.

EXPERIMENT 13.—Dog 209; Nov. 28, 1921. Irradiation at 11:30 a. m.

		Kottmann Reaction	
Sample 1:	Blood before irradiation	2.0	
" 2:	1 hour after irradiation	2.0	
" 3:	1 day after irradiation	1.5	
" 4:	2 days after irradiation	1.75	
" 5:	3 days after irradiation	1.75	
" 6:	4 days after irradiation	1.75	
" 7:	5 days after irradiation	1.75	
" 8:	7 days after irradiation	0.5	
" 9:	9 days after irradiation	0.0	
" 10:	12 days after irradiation	0.0	Killed

It will be observed that in this case the evidence of increase in the thyroid activity was not apparent until about seven days after the irradiation, if we exclude the transient alteration that was apparent twenty-four hours after the raying.

Irradiation of Other Regions: Liver.—During the course of the work it seemed probable that any cellular destruction that would entail the accumulation of the products of tissue destruction in the blood stream might influence the Kottmann reaction. With a large dose of roentgen-rays we might anticipate the presence of such fragments derived from the cellular destruction of the liver parenchyma. An experiment was made to determine the point.

EXPERIMENT 14.—Dog 234; Dec. 12, 1921. Liver area rayed for a total of forty-five minutes; no filter; 5 inch spark gap; 3 ma.; 10 inch focal distance.

		Kottmann Reaction
Sample 1:	Before irradiation	2.0
" 2:	1 hour after irradiation	2.0
" 3:	4 hours after irradiation	1.5
" 4:	1 day after irradiation	1.4
" 5:	3 days after irradiation	1.0
" 6:	6 days after irradiation	1.0
" 7:	9 days after irradiation	1.5

Here again the reaction observed is not of the type seen with exophthalmic serums, because the delay in the serum reaction is transient; after 5 minutes the color in the tubes is usually equalized.

Chloroform Necrosis of the Liver.—That the reaction is delayed when the liver is injured by other methods was observed when we produced a chloroform necrosis of the liver in dogs (two days starvation; one hour chloroform anesthesia). The serum from these animals examined two days after the anesthesia was bile stained and the Kottmann reaction was considerably retarded.

The experiments make probable the assumption that any extensive tissue injury may bring about serum alterations similar in character to those produced in hyperthyroidism. It is, of course, not excluded that irradiation of this kind and other related injuries may mobilize sub-

stances which, on entering the blood stream, may stimulate the thyroid gland. We are of the impression that the first explanation is the correct one.

Effect of Bacterial Intoxication.—In order to determine the effect of a severe intoxication (produced by the injection of colon bacilli) the following experiment was carried out:

EXPERIMENT 15.—Dog 233; Dec. 21, 1921; weight, 13.2 kg.; injected intravenously with 500 mg. (moist weight) of a fresh culture of colon bacilli, at 10:30 a. m.

		Kottmann Reaction
Sample 1:	Before injection	1.25
" 2:	30 minutes after injection	0.7
" 3:	1 hour and 30 minutes after injection	0.0
" 4:	3 hours and 30 minutes after injection	0.62

Effect of Peptone Injection.—

EXPERIMENT 16.—Dog 231; weight, 7.5 kg.; injected with 2 gm. Witte peptone intravenously at 10:35 a. m.

		Kottmann Reaction
Sample 1:	Before injection	1.9
" 2:	10 minutes after injection	
	Serum flocculates when hydrochonin is added	
" 3:	1 hour after injection	1.3
" 4:	4 hours after injection	1.6

The animal was in shock for about thirty minutes after the injection, but made a complete recovery within an hour. The reaction was somewhat delayed.

Effect of Peptone Ingestion.—

EXPERIMENT 17.—Dog 237; weight, 8 kg.; given 50 gm. Armour's peptone by mouth at 10 a. m.

		Kottmann Reaction	Leukocyte Count
Sample 1:	Before injection	2.0	12,000
" 2:	30 minutes later	2.0	14,300
" 3:	1 hour and 30 minutes later	1.7	40,000
" 4:	4 hours later	1.8	28,400
" 5:	24 hours later	1.9	14,000

While the animal reacted with a distinct leukocytosis, the Kottmann reaction was not altered to any marked extent, only a slight retardation being apparent.

Effect of Trypsin Ingestion.—

EXPERIMENT 18.—Dog 182; 15 gm. trypsin (in the form of enteric pills) was placed directly into the small intestines through a small enterostomy opening.

The effect on the serum was studied at the following intervals:

		Kottmann Reaction
Sample 1:	Before administration of trypsin	1.1
" 2:	2 hours after	1.4
" 3:	4 hours after	1.1
" 4:	6 hours after	0.4
" 5:	10 hours after	1.0
" 6:	24 hours after	1.4

In another experiment trypsin in solution was injected directly into the small intestine in the same dog at 11:30 a. m. (20 gm.).

EXPERIMENT 19.—Dog 182. The serum was studied at the following intervals:

		Kottmann Reaction
Sample 1:	Before injection	1.1
" 2:	1 hour later	1.1
" 3:	2 hours later	0.4
" 4:	4 hours later	0.9
" 5:	8 hours later	0.6
" 6:	24 hours later	1.2

Effect of Hemorrhage on the Kottmann Reaction.—

EXPERIMENT 20.—Dog 184; weight, 7 kg. Bled as follows:

		Kottmann Serum
Sample 1:	100 c.c.	2.0
" 2:	100 c.c. 1 hour later	1.6
" 3:	100 c.c. 2 hours later	1.6
" 4:	60 c.c. 3 hours later	1.4
" 5:	80 c.c. 4 hours later	1.0

EXPERIMENT 21.—Dog 199; 9,600 gm. Bled as follows:

		Kottmann Serum	Plasma
Sample 1:	300 c.c.	1.25	1.25
" 2:	80 c.c. 1 hour later	1.5	0.85
" 3:	80 c.c. 2 hours later	1.25	0.5
" 4:	80 c.c. 3 hours later	0.7	0.0

EXPERIMENT 22.—Dog 200; 8,100 gm. Bled as follows:

		Kottmann Serum
Sample 1:	100 c.c.	1.7
" 2:	100 c.c. 1 hour later	1.7
" 3:	100 c.c. 2 hours later	1.4
" 4:	100 c.c. 3 hours later	0.5

EXPERIMENT 23.—Dog 238; the reaction was not altered.

EXPERIMENT 24.—Dog 265; 21,000 gm.; bled as follows:

		Kottmann Serum
Sample 1:	500 c.c. 10 a. m.	1.5
" 2:	50 c.c. 10:30 a. m.	1.5
" 3:	50 c.c. 11 a. m.	2.0
" 4:	50 c.c. 1 p. m.	2.0
" 5:	50 c.c. 4 p. m.	1.5
" 6:	50 c.c. 11 a. m. following day	1.0

Exercise.—The effect of exercise on the Kottmann reaction was studied. An electrically driven treadmill was used in which the dogs were placed for two hour runs. The serum showed no alteration with exercise of this degree.

When the duration of the experiment was prolonged, some effect was observed, as is shown in the following experiment.

EXPERIMENT 25.—Dog 235; Dec. 29, 1921.

		Kottmann Serum
Sample 1:	Before	2.0
	(Treadmill six hours, about 90,000 feet)	
" 2:	Immediately after exercise	1.75
" 3:	Following morning	1.0

While the effect seemed apparent in the direction of retardation, this was never marked and could by no means be compared to the retardation obtained with exophthalmic serums.

DISCUSSION

Inasmuch as we were able to confirm the clinical usefulness [1] of the Kottmann reaction in making apparent certain alterations in thyroid activity associated with hyperthyroidism, we have in these experiments sought to determine whether the reaction indicated the presence of the thyroid secretion in the blood, or whether the active substance of the gland brought about alterations in the tissue metabolism, which then became manifest in an indirect way in the Kottmann reaction.

Our experiments support this latter contention. Apart from the fact that when thyroxin is directly added to serum, the Kottmann reaction is not retarded, we found that injection into animals was not followed by an immediate change in the reaction, but that a period of several days elapsed (from three to five) before the effect of the injection became apparent in the serum. This corresponds with the clinical experience that with injection of thyroxin the maximum effect does not become apparent for a number of days, but then may persist for ten days or more. This corresponds with the effect on the Kottmann reaction observed in dogs.

We have, furthermore, been able to demonstrate that following irradiation of the thyroid region with moderate doses of roentgen rays a similar effect may be brought about. This observation, too, coincides with the frequent clinical observation of thyroid activation during the course of roentgen-ray irradiation of the gland as a therapeutic measure.

Massage of the hypertrophied gland in dogs also results in a retardation of the serum reaction three or four days after the massage. In the single experiment with massage of a normal gland some retardation was also observed, but not to the same extent as with the goiter dogs.

Other experiments which were made (massive roentgen-ray irradiation of the liver, peptone shock, bacterial shock, hemorrhage, etc.) were all followed by definite serum alteration, usually in the direction of a retardation of the reaction. This we believe is in these cases brought about by an alteration in the globulin ratio of the serum, as well as alterations in the hydrogen ion balance, a subject which will be taken up in a subsequent paper.

It is evident from the results of these experiments that the alterations in the reaction with serum obtained under different experimental conditions need not be associated with thyroid dysfunction. The thyroid dysfunction alters cellular metabolism and this, in turn, alters the physical properties of the serum so that in cases of hyperthyroidism the serum is a better protective agent than normally. If the cellular

metabolism is altered by other insults, serum alterations must also take place and these will be reflected in the Kottmann reaction. It is needless to emphasize that for general clinical work great weight need not be attached to changes other than those involved in thyroid dysfunction, because we have not found that they alter the reaction (in dogs) to a degree comparable with the alterations produced in thyroid disturbances in clinical material.

We have observed that dog serum when standing for several days in the refrigerator loses its protective power to a considerable extent, differing in this from serums obtained from cases of hyperthyroidism, which have been kept for several weeks with only a partial loss of their protective property. Comparative tests made with dog serum must therefore always be made on fresh serum under strictly uniform conditions.

CONCLUSIONS

1. In clinical cases of hyperthyroidism the Kottmann reaction may return to normal after thyroidectomy. Fright, on the other hand, produced a positive reaction in two patients; in control patients who were subjected to similar trauma, but who were not frightened (one unconscious, one semiconscious, the other conscious and calm) the reaction was within normal limits.

2. Experimentally it has been found that thyroxin injections, irradiation and massage of the hypertrophied gland resulted in an increased protective property of the serum which became manifested in the course of several days. The serum alteration is, therefore, not a direct one, but is evidently the result of alterations in cellular metabolism brought about by the increased thyroid activity.

3. Other experimental procedures may alter the reaction (bacterial shock, peptone shock, trypsin ingestion, hemorrhage, irradiation of remote organs). In no case was the delay in the reaction comparable to that observed with exophthalmic serums and we do not believe that the alterations in the reactions observed under these experimental conditions will detract from the clinical usefulness of the test in the diagnosis and the control of the therapy of thyroid dysfunction.

THE GLUCOSE MOBILIZATION RATE IN HYPERTHYROIDISM *

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In a preliminary paper [1] on this subject the results of some observations on the glucose mobilization rate in hyperthyroidism were reported. In this paper the results will be exhibited in greater detail. Ten normal controls and ten well marked cases of exophthalmic goiter have been studied under identical conditions. All the cases of hyperthyroidism were of the same type, i. e., exophthalmic goiter, with all the clinical manifestations of a well marked thyrotoxicosis.

The object of the experiments was to obtain some insight into the mechanism of so-called decreased carbohydrate tolerance in cases of hyperthyroidism. Through studies of the change in the blood sugar, the respiratory quotient and the total metabolism, before and after glucose ingestion, we derived our data for computing the carbohydrate utilization.

The procedure need not be gone over again in detail as it was clearly outlined in the preliminary paper. A Tissot spirometer, equipped with a Siebe-Gorman half face mask and Douglas valves, and a Haldane gas analysis apparatus, were used routinely in all the experiments under the standard technic for this type of work. Samples of the total expired air were taken over mercury in a special sampling tube for analysis. All technical results and calculations were carefully checked over, and all sources of error eliminated, in so far as it was possible. Altogether the experiment occupied about three and one-half hours. The fasting patient was put to rest for from one-half to three-quarters of an hour after which a basal period was run. The mask was then replaced for a second basal period. The basal respiratory quotient and total metabolism used in our calculations were the average of these two periods. As soon as these were completed, blood was taken for a fasting blood sugar, and the glucose was given in a mixture of grapefruit juice—for the most part the dosage was 1.75 gm. per kilogram body weight.[2] In one or two of the first experiments 100 gm. was given without regard to weight. Fifteen minutes after the ingestion of the glucose, the blood sugar was taken, and five minutes later (i. e., twenty minutes after glucose ingestion), the mask was replaced for

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1. Sanger, B. J.: Proc. Soc. Exper. Biol. & M. **17**:117, 1921.
2. Janney and Isaacson: J. A. M. A. **70**:1131 (April 20) 1918.

the first postglucose period. The duration of the periods was usually ten minutes. This made the first period end on the half hour after the taking of the glucose. From then on until the end of the experiment a period was run every half hour, making in all five postglucose periods. Blood was withdrawn again one hour and two hours after the glucose ingestion. This gave us two basal periods and five postglucose periods, and four samples of blood for analysis. A specimen of urine taken at the end of the experiment was tested for glucose. With the data obtained, the calculations were made and tabulated.

The comparison of the change in the metabolic rate between the normals and the cases of hyperthyroidism was very confusing. The percentage rise above basal was much less in the cases of exophthalmic goiter than in the controls, but if the abnormal cases were figured on the basis of what the rise in calories would have amounted to had the patient's basal metabolism been normal, then the results were very

TABLE 1.—Blood Sugar Curves in Normal Controls

	Name										Aver-
	C.L.	H.D.	W.V.G.	E.H.	B.S.	M.C.	M.C.	H.J.	R.Mc.	H.R.G.	age
Fasting	0.89	0.83	0.91	0.92	0.80	0.87	0.72	1.10	0.92	Lost	0.85
15 minutes	0.98	1.05	1.19	1.37	1.09	1.10	1.24	1.20	1.03	0.76	
60 minutes	1.30	1.08	0.93	1.51	1.35	1.26	1.54	1.67	1.40	0.78	
120 minutes	0.95	0.95	1.10	1.14	1.15	1.17	1.20	1.20	1.03	0.73	
Range	0.41	0.25	0.28	0.59	0.55	0.39	0.82	0.57	0.48	....	0.48

TABLE 2.—Blood Sugar Curves in Cases of Hyperthyroidism

	Name										Aver-
	F.B.	H.G.	F.K.	C.E.	L.M.	A.S.	M.D.	G.S.	B.S.	E.R.	age
Fasting	0.91	0.95	1.02	1.03	0.93	1.13	0.91	1.00	1.12	0.94	0.99
15 minutes	1.3	1.25	1.54	1.40	1.37	2.00	1.50	1.40	1.74	1.30	
60 minutes	2.10	2.30	2.32	2.04	1.80	2.32	1.90	1.80	2.10	1.50	
120 minutes	1.85	2.30	2.00	1.50	1.30	1.07	1.06	1.04	1.40	1.07	
Range	0.94	1.35	1.30	1.01	0.87	1.19	0.99	0.80	0.98	0.56	1.00

similar to those obtained in the normal controls. It seems likely, therefore, that the specific dynamic action of carbohydrates is much the same in cases of hyperthyroidism and in normal persons.

Taking as a normal blood sugar curve, one that has a fasting level from 0.7 to 1.1 gm. per liter, that reaches its peak in one hour after glucose ingestion, rarely going higher than 1.7, and which tends to reach its fasting level within two hours, then our ten normal controls were well within this range (Table 1).

In no case did glucose appear in the urine.

The cases of hyperthyroidism showed essentially normal fasting blood sugars, though on the average they were somewhat higher than the fasting values found in the normals (Table 2). The range in the great majority of cases studied, however, was quite different. There

was a distinct rise after fifteen minutes, but the peak was not reached until after one hour when it was distinctly above the normal range. The blood sugar, in the great majority of cases, remained distinctly elevated after two hours. There was one notable exception to this in one case (E. R., a very distinct case of exophthalmic goiter), in which the blood sugar curve was entirely normal. At the time of the test this patient had auricular fibrillation which was almost certainly secondary to the thyrotoxicosis, as it cleared up entirely (electrocardiograph evidence) under treatment. This rather strikingly normal curve in a well marked case, along with one or two other cases in the series that were within normal variation, showed that all cases of hyperthyroidism do not have deranged carbohydrate metabolism if judged by blood sugar curves alone. Five of the cases showed glycosuria after the glucose ingestion, three were sugar free and two were not tested through error.

TABLE 3.—CURVES OF RESPIRATORY QUOTIENT IN NORMAL CONTROLS

	Name										Average
	C.L.	H.D.	W.V.G.	E.H.	B.S.	M.C.	M.C.	H.J.	R.Mc.	H.R.G.	
Basal	0.78	0.83	0.75	0.77	0.78	0.79	0.83	0.85	0.83	0.75	0.80
30 minutes	0.82	0.81	0.84	0.80	0.80	0.82	0.83	0.83	0.88	0.79	
60 minutes	0.80	0.80	0.88	0.80	0.84	0.88	0.86	0.84	0.84	0.81	
90 minutes	0.89	0.88	0.88	0.90	0.86	0.89	0.83	0.88	0.88	0.86	
120 minutes	0.87	0.88	0.84	0.92	0.88	0.92	0.92	0.96	0.96	0.83	
150 minutes	0.94	0.90	0.90	0.90	0.86	0.93	0.90	0.89	0.92	0.87	
Range	0.16	0.09	0.15	0.15	0.10	0.14	0.09	0.10	0.10	0.12	0.12

TABLE 4.—CURVES OF RESPIRATORY QUOTIENT IN CASES OF HYPERTHYROIDISM

	Name										Average
	F.B.	H.G.	F.K.	C.E.	L.M.	A.S.	M.D.	G.S.	B.S.	E.R.	
Basal	0.75	0.76	0.76	0.75	0.75	0.74	0.79	0.79	0.81	0.72	0.76
30 minutes	0.84	0.79	0.81	0.84	0.88	0.83	0.82	0.79	0.88	0.76	
60 minutes	0.90	0.86	0.90	0.92	0.98	0.84	0.97	0.94	0.92	0.83	
90 minutes	0.91	0.91	0.92	1.00	0.97	0.88	0.97	1.00	0.97	0.85	
120 minutes	0.94	0.90	0.94	1.03	0.96	0.85	0.98	0.98	0.95	0.92	
150 minutes	0.99	0.92	0.94	1.05	0.95	0.89	0.97	0.96	0.96	0.89	
Range	0.24	0.16	0.18	0.30	0.23	0.15	0.19	0.21	0.16	0.20	0.20

The respiratory quotients when studied in phases offered the most interesting data in our experiments. The basal quotient on the average in the cases of hyperthyroidism was slightly lower than in the normal controls—0.76 as compared to 0.80 (Tables 3 and 4). In the cases of exophthalmic goiter after the dose of glucose had been given, the quotients rose rapidly to a high figure, in one case going as high as 1.05, whereas in the normal cases, the quotients rose more slowly, and did not reach nearly so high a point. The high level of the respiratory quotient was maintained for a longer time in the cases of hyperthyroidism than in the normal controls, and at the end of the two and one-half hours was still very high. The average range from the basal to the peak in the cases of hyperthyroidism was twenty points,

while that in the normals was only twelve, the greatest being thirty in the one and sixteen in the other. This proves very strikingly that individuals with thyrotoxicosis can burn carbohydrate readily, in fact, do burn it with avidity, and along with the fact that their blood sugar stays high suggests very probably that there is an inability for storing carbohydrate in these cases. For if they burn it more rapidly than do normals, and in spite of this maintain a high blood sugar, then obviously they cannot be storing it. There is good experimental evidence to substantiate this view.[3]

From the figures of the respiratory quotient we derived our calculations for the utilization of carbohydrate. Fifteen per cent. was deducted from the total calories per hour for that portion of the heat derived from protein metabolism.[4] The remaining calories were assumed as coming from carbohydrate and fat, and were apportioned to each of these metabolites according to the percentage tables of Zunst and Schumburg as modified by Riche and Lusk. The respiratory quotients were used directly without deductions for protein metabolism as derived from the urinary nitrogen, that is, they were not nonprotein respiratory quotients. For practical purposes of comparison this seemed adequate, though we realized that nitrogen studies would have made our data somewhat more accurate. The difficulty of collecting specimens over short periods, however, and the uncertainty of the nitrogen in the urine collected representing the protein utilized during the period of the experiment, due to the nitrogen lag, decided us to leave urinary studies out of our work. Tables 5 and 6 show the calculations in each case.

It is evident that in the normal cases following the dose of glucose, there was an increase in the number of grams of carbohydrate utilized over the amount utilized at basal. This increase, however, was only a small proportion of the quantity ingested, the total for the two and one-half hours following the ingestion of the dose being on the average 18.1 per cent. of the amount taken (Table 7). This, plus the rapid rise and fall in the blood sugar, makes us feel that in these cases the greater part of the carbohydrate is stored.

In the cases of hyperthyroidism, on the other hand, an average of 36.1 per cent. (Table 8) of the amount ingested was burned over the same period (two and one-half hours) and at the end of this period the blood sugar was still greatly elevated. The amount of carbohydrate accounted for by this increased blood sugar is very small, only amounting to a few grams, but when we realize that the maintained high concentration of sugar in the blood means a high concentration of sugar in the tissues, this figure is more significant.

3. Cramer and Krause: Proc. Roy. Soc., Ser. B. **86**:50, 1913. Kuriyama: J. Biol. Chem. **33**:193, 1918.
4. Voit, E.: Ztschr. f. Biol. **41**:188, 1901.

TABLE 5.—Data on Ten Normal Controls After Glucose Ingestion

	Respiratory Quotient	Calories per Hr.	Rise, Calories per Hr.	Calories per Sq. M. per Hr.	Per Cent Rise Above Basal	Per Cent. Rise Above Normal	Calories from Carbohyd. and Fat*	Per Cent. Calories from Carbohyd.	Calories from Carbohyd.	Gm. Carbohydrate Utilized		Blood Sugar, Gm. per Liter
										Total	Increase	
C. L., ♂, 26 Ht., 176.9 Cm. Wt., 65 Kg. Dose of glucose, 114 Gm.												
Basal	0. 8	65.5	0	36.4	0	0	55.7	25.2	14.0	3.4	...	0.89
Post glucose:												
30 minutes	0.82	73.8	8.3	41.0	13	12	62.7	38.8	24.3	5.9	2.5	0.98†
60 minutes	0.80	73.2	7.7	40.6	12	11	62.2	32.0	19.9	4.9	1.5	1.3
90 minutes	0.19	70.7	5.2	39.3	8	7	60.2	62.6	37.7	9.2	5.8	
120 minutes	0 87	66.3	0.8	36.9	1	0	56.4	55 8	31.4	7.7	4.3	0.95
150 minutes	0.94	68.9	3 4	38.3	5	5	58.6	79.6	46.6	11.4	8.0	
H. D., ♂, 26 Ht., 175.2 Cm. Wt., 68 Kg. Dose of glucose, 120 Gm.												
Basal	0.83	67.1	0	36.7	0	0	57.4	42.2	24.2	5 9	...	0.83
Post glucose:												
30 minutes	0.81	74.6	7.5	40.8	11	10	63.4	35.4	22.4	5.5	—0.4	1.05†
60 minutes	0 80	71.7	4.6	39.2	6	6	60.9	32.0	19.5	4.8	—1.1	1.08
90 minutes	0.88	0.75	7.9	41.0	11	11	63.8	59.2	37.8	9.2	3.3	
120 minutes	0 88	79.8	12.7	43.6	18	17	67.8	59.2	40.1	9.8	3.9	0.95
150 minutes	0.90	77.3	10.2	42.2	14	14	65.7	66.0	43.4	10.6	4.7	
W. V. G., 32 Ht., 185.6 Cm. Wt., 71.9 Kg. Dose of glucose, 126 Gm.												
Basal	0.75	77.3	0	39.8	0	0	65.7	15.0	9.9	2.4	...	0 91
Post glucose:												
30 minutes	0 84	84.7	7.4	43.7	10	10	72.0	45.6	32.8	8.0	5.6	1.19†
60 minutes	0 88	86.3	9.0	44.5	12	12	73.4	59.2	43.4	10.6	8.2	0.93
90 minutes	0 88	89.7	12.4	46.2	16	17	76.2	59.2	45.1	11.0	8.6	
120 minutes	0.84	89.7	12.4	46.3	16	17	76.2	45.6	34.7	8 5	6.1	1.1
150 minutes	0.90	82.5	5.2	42.5	7	8	70.1	66.0	46.3	11.3	8.9	
F. H., ♀, 23 Ht., 171.1 Cm. Wt., 52 Kg. Dose of glucose, 91 Gm.												
Basal	0.77	55.1	0	34.4	0	0	46.8	21.8	10.2	2.5	...	0.92
Post glucose:												
30 minutes	0.80	59.8	4.7	37.4	9	8	50.8	32.0	16.3	4.0	1.5	1.37†
60 minutes	0.80	60.8	5.7	38.0	10	10	51.7	32.0	16.6	4.0	1.5	1.51
90 minutes	0.90	63.4	8.3	39.6	15	14	53.9	66.0	35.6	8.7	6 2	
120 minutes	0.92	65.4	10.3	40.9	19	18	55.6	72.8	40.5	9.9	7.4	1.14
150 minutes	0.90	63.1	8.0	39.5	15	14	53.6	66.0	35.4	8.6	6.1	
B. S., 29 Ht., 169 Cm. Wt., 51.6 Kg. Dose of glucose, 90 Gm.												
Basal	0.78	51.8	0	32.8	0	0	44.0	25.2	11.1	2.7	...	0.8
Post glucose:												
30 minutes	0.80	56.9	5.1	36.0	10	8	48.4	32.0	15.5	3.8	1.1	1.09†
60 minutes	0.84	59 0	7.2	37.3	14	11.4	50.2	45.6	22.9	5.6	2 9	1.35
90 minutes	0.86	57.8	6.0	36.6	12	9.6	49.1	52.4	25.7	6.3	3.6	
120 minutes	0.88	60 4	8.6	38.2	16	13.7	51.3	59.2	30.4	7.4	4.7	1.15
150 minutes	0.86	56.1	4.3	35.5	8	6.8	47.7	52.4	25.0	6.1	3.4	
M. C., ♀, 25 Ht., 154.4 Cm. Wt., 51 Kg. Dose of glucose, 80 Gm.												
Basal	0.79	52.9	0	36.0	0	0	45.0	28.6	12.9	3.1	...	0.87
Post glucose:												
30 minutes	0.82	55.2	2.3	37.6	4	4	46.9	38.8	18.2	4.4	1.3	1.1†
60 minutes	0.88	53.6	0.7	36.5	1	1	45.6	59.2	27.0	6.6	3.5	1.26
90 minutes	0.89	55.3	2.4	37.6	4	4	47.0	62.6	29.4	7.2	4.1	
120 minutes	0.92	53.7	0.8	36.5	1	1	45.6	72.8	33.2	8.1	5.0	1.17
150 minutes	0.93	54.5	1.6	37.1	3	3	46.3	76.2	35.3	8.6	5.5	

* 15 per cent. deducted from calories per hour for calories from (nitrogen) protein.
† Blood sugar 15 minutes post glucose.

TABLE 5.—Data on Ten Normal Controls After Glucose Ingestion—(*Continued*)

	Respiratory Quotient	Calories per Hr.	Rise, Calories per Hr.	Calories per Sq. M. per Hr.	Per Cent. Rise Above Basal	Per Cent. Rise Above Normal	Calories from Carbohyd. and Fat*	Per Cent. Calories from Carbohyd.	Calories from Carbohyd.	Gm. Carbohydrate Utilized: Total	Gm. Carbohydrate Utilized: Increase	Blood Sugar, Gm. per Liter
M. C., ♂, 25 Ht., 171.6 Cm. Wt., 53.5 Kg. Dose of glucose, 95 Gm.												
Basal	0.83	62.0	0	38.0	0	0	52.7	42.2	22.2	5.4	...	0.72
Post glucose:												
30 minutes	0.83	64.8	2.8	39.7	4	4	55.1	42.2	23.3	5.7	0.3	1.24†
60 minutes	0.86	64.4	2.4	39.5	4	4	54.7	52.4	28.7	7.0	1.6	1.54
90 minutes	0.83	65.1	3.1	39.9	5	5	55.3	42.2	23.3	5.7	0.3	
120 minutes	0.92	65.5	3.5	40.2	6	6	55.7	72.8	40.6	9.9	4.5	1.2
150 minutes	0.90	65.2	3.2	40.0	5	5	55.4	66.0	36.6	8.9	3.5	
H. J., 22 Ht., 170.9 Cm. Wt., 63 Kg. Dose of glucose, 110 Gm.												
Basal	0.85	66.9	0	38.4	0	0	56.9	49.0	27.8	6.77	...	1.1
Post glucose:												
30 minutes	0.83	72.7	5.8	41.8	9	8.6	61.8	42.2	26.1	6.37	—0.4	1.2†
60 minutes	0.84	73.6	6.7	42.3	10	9.8	62.6	45.6	28.6	6.97	0.2	1.67
90 minutes	0.88	71.7	4.8	41.2	7	7	60.9	59.2	36.0	8.8	2.03	
120 minutes	0.93	73.7	6.8	42.3	10	9.8	62.6	76.2	47.7	11.6	4.8	1.2
150 minutes	0.89	71.5	4.6	41.1	7	7	60.8	62.6	38.1	9.3	2.5	
R. Mc., 22 Ht., 181.5 Cm. Wt., 78.5 Kg. Dose of glucose, 137 Gm.												
Basal	0.83	66.7	0	33.5	0	0	56.7	42.2	23.9	5.8	...	0.92
Post glucose:												
30 minutes	0.88	74.3	7.6	37.3	11	10	63.2	59.2	37.4	9.1	3.3	1.03†
60 minutes	0.84	76.9	10.2	38.6	15	13	65.4	45.6	29.8	7.3	1.5	1.4
90 minutes	0.89	78.2	11.5	39.9	17	15	66.5	61.0	40.5	9.9	4.1	
120 minutes	0.93	75.3	8.6	37.8	13	11	64.0	76.2	48.7	11.9	6.1	1.03
150 minutes	0.92	77.9	11.2	39.1	17	14	66.2	72.8	48.2	11.8	6.0	
H. R. G., ♂, 36 Ht., 172 Cm. Wt., 70.7 Kg. Dose of glucose, 100 Gm.												
Basal	0.75	65.3	0	35.5	0	0	55.5	15.0	8.3	2.0		Lost
Post glucose:												
30 minutes	0.79	69.3	4.0	37.7	6	6	58.9	28.6	16.8	4.1	2.1	0.76†
60 minutes	0.81	69.3	4.0	37.6	6	6	58.9	35.4	20.8	5.1	3.1	0.78
90 minutes	0.86	73.6	8.3	40.0	12	11	62.6	52.4	32.8	8.0	6.0	
120 minutes	0.83	70.8	5.5	38.5	8	8	60.2	42.2	25.4	6.2	4.2	0.73
150 minutes	0.87	72.8	7.5	39.5	11	10	61.9	55.8	34.6	8.4	6.4	

* 15 per cent. deducted from calories per hour for calories from (nitrogen) protein.
† Blood sugar 15 minutes post glucose.

The explanation seems obvious. In cases of hyperthyroidism there is a deficiency in the ability to store carbohydrate. This makes for a carbohydrate plethora and the carbohydrate plethora stimulates carbohydrate metabolism. This inability to store carbohydrate appears to be the only logical explanation of the carbohydrate plethora, as it cannot be due to the inability of the tissues to utilize it in this condition. Besides, this explanation fits in with the experimental evidence, as Cramer and his collaborators and Kuriyama have shown that thyroid

TABLE 6.—Data on Ten Cases of Hyperthyroidism in Which Glucose Was Administered

	Respiratory Quotient	Calories per Hr.	Rise, Calories per Hr.	Calories per Sq. M. per Hr.	Per Cent. Rise Above Basal	Per Cent. Rise Above Normal	Calories from Carbohyd. and Fat*	Per Cent. Calories from Carbohyd.	Calories from Carbohyd.	Gm. Carbohydrate Utilized		Blood Sugar, Gm. per Liter
										Total	Increase	
F. B., 32 Ht., 174 Cm. Wt., 53.8 Kg. Dose of glucose, 94.1 Gm.												
Basal	0.75	95.0	0	58.0	0	0	80.8	15.0	12.1	3.0	...	0.91
Post glucose:												
30 minutes	0.84	104.3	9.3	63.6	9	14	88.6	45.6	40.5	9.9	6.9	1.3 †
60 minutes	0.90	104.3	9.3	63.6	9	14	88.6	66.0	58.5	14.2	11.2	2.1
90 minutes	0.91	106.2	11.2	64.7	11	18	90.3	69.4	62.5	15.2	12.2	
120 minutes	0.94	105.3	10.3	64.2	10	17	89.5	79.6	71.4	17.4	14.4	1.85
150 minutes	0.99	103.2	8.2	62.9	8	13	87.7	96.6	84.9	20.6	17.6	
H. G., 22 Ht., 160.5 Cm. Wt., 47.8 Kg. Dose of glucose, 84 Gm.												
Basal	0.76	85.9	0	58.0	0	0	73.0	18.4	13.4	3.3	...	0.95
Post glucose:												
30 minutes	0.79	93.4	7.5	63.1	9	13	79.4	28.6	22.7	5.5	2.2	1.25 †
60 minutes	0.86	89.6	3.7	60.5	4	6	76.2	52.4	39.9	9.7	6.4	2.3
90 minutes	0.91	89.7	3.8	60.6	4	6	76.3	69.4	53.0	12.9	9.6	
120 minutes	0.90	90.1	4.2	60.9	5	7	76.6	66.0	50.6	12.3	9.0	2.3
150 minutes	0.92	90.1	4.2	60.9	5	7	76.6	72.8	55.8	13.6	10.3	
F. K., 24 Ht., 145 Cm. Wt., 37 Kg. Dose of glucose, 65 Gm.												
Basal	0.76	68.7	0	56.0	0	0	58.4	18.4	10.7	2.6	...	1.02
Post glucose:												
30 minutes	0.81	67.5	−1.2	54.9	−2	−3	57.4	35.4	20.6	5.0	2.4	1.54 †
60 minutes	0.90	71.1	2.4	57.8	3	5	60.4	66.0	39.9	9.7	7.1	2.32
90 minutes	0.92	64.9	−3.8	52.8	−6	−9	55.1	72.8	40.1	9.8	7.2	
120 minutes	0.94	67.3	−1.4	54.7	−2	−3	57.2	79.6	45.5	11.1	8.5	2.0
150 minutes	0.94	59.2	−9.5	48.1	−14	−21	50.3	79.6	40.0	9.8	7.2	
C. E., 30 Ht., 169 Cm. Wt., 52.5 Kg. Dose of glucose, 92 Gm.												
Basal	0.75	80.2	0	50.5	0	0	68.2	15.0	10.2	2.5	...	1.03
Post glucose:												
30 minutes	0.84	89.3	9.1	56.1	11	15	75.9	45.6	34.6	8.4	5.9	1.4 †
60 minutes	0.925	80.5	0.3	50.6	0	0	68.4	74.0	50.6	12.3	9.8	2.04
90 minutes	1.00	87.9	7.7	55.3	9	13	74.7	100.0	74.7	18.2	15.7	
120 minutes	1.03	91.2	11.0	57.4	14	19	77.5	100.0	77.5	18.9	16.4	1.5
150 minutes	1.05	87.5	7.3	55.1	9	12	74.5	100.0	74.5	18.2	15.7	
L. M., ♀, 44 Ht., 153 Cm. Wt., 46.6 Kg. Dose of glucose, 82 Gm.												
Basal	0.75	78.7	0	55.8	0	0	66.9	15.0	10.0	2.4	...	0.93
Post glucose:												
30 minutes	0.88	90.3	11.6	64.0	15	23	76.8	59.2	45.5	11.1	8.7	1.37 †
60 minutes	0.98	89.4	10.7	63.4	14	21	76.0	93.2	70.8	17.3	14.9	1.8
90 minutes	0.97	86.2	7.5	61.1	10	15	73.3	89.8	65.8	16.0	13.6	
120 minutes	0.96	82.2	3.5	58.3	4	7	69.9	86.4	60.4	14.7	12.3	1.3
150 minutes	0.95	79.5	0.8	56.4	1	2	67.6	83.0	56.1	13.7	11.3	
A. S., ♀, 43 Ht., 169.5 Cm. Wt., 41 Kg. Dose of glucose, 72 Gm.												
Basal	0.74	86.9	0	60.8	0	0	73.9	11.6	8.6	2.1	...	1.13
Post glucose:												
30 minutes	0.83	95.0	8.1	66.5	9	16	80.8	42.2	34.1	8.3	6.2	2.0 †
60 minutes	0.84	91.7	4.8	64.1	5	9	78.0	45.6	35.6	8.7	6.6	2.32
90 minutes	0.88	90.1	3.2	63.0	4	6	76.6	59.2	45.3	11.0	8.9	
120 minutes	0.85	87.6	0.7	61.3	1	1	74.5	49.0	36.5	8.9	6.8	1.07
150 minutes	0.89	84.7	−2.2	59.2	−2	−4	72.0	62.6	45.1	11.0	8.9	

* 15 per cent. deducted from calories per hour for calories from (nitrogen) protein.
† Blood sugar 15 minutes post glucose.

TABLE 6.—Data on Ten Cases of Hyperthyroidism in Which Glucose Was Administered—(*Continued*)

	Respiratory Quotient	Calories per Hr.	Rise, Calories per Hr.	Calories per Sq. M. per Hr.	Per Cent. Rise Above Basal	Per Cent. Rise Above Normal	Calories from Carbohyd. and Fat*	Per Cent. Calories from Carbohyd.	Calories from Carbohyd.	Gm. Carbohydrate Utilized: Total	Gm. Carbohydrate Utilized: Increase	Blood Sugar, Gm. per Liter
M. D., 30 Ht., 164.5 Cm. Wt., 57.3 Kg. Dose of glucose, 100 Gm.												
Basal	0.79	87.1	0	53.8	0	0	74.1	28.6	21.1	5.1	...	0.91
Post glucose:												
30 minutes	0.82	89.8	2.7	55.4	3	4	76.3	38.8	29.6	7.2	2.1	1.5†
60 minutes	0.97	93.8	6.7	57.9	7.6	11	79.7	89.8	71.5	18.3	13.2	1.9
90 minutes	0.97	91.9	4.8	56.7	5	8	78.1	89.8	70.3	17.1	12.0	
120 minutes	0.98	91.4	4.3	56.4	5	7	77.7	93.2	72.5	17.7	12.6	1.66
150 minutes	0.97	89.0	1.9	54.9	2	3	75.6	89.8	67.8	16.5	11.4	
G. S., ♀, 26 Ht., 157.5 Cm. Wt., 49.8 Kg. Dose of glucose, 88 Gm.												
Basal	0.79	76.7	0	52.2	0	0	65.2	28.6	18.6	4.5	...	1.0
Post glucose:												
30 minutes	0.79	86.6	9.9	58.9	13	18	73.6	28.6	21.1	5.1	0.6	1.4†
60 minutes	0.94	84.2	7.5	57.3	10	14	71.6	79.6	57.0	13.9	9.4	1.8
90 minutes	1.00	83.4	6.7	56.8	9	12	70.9	100.0	70.9	17.3	12.8	
120 minutes	0.98	79.3	2.6	53.9	3	5	67.4	93.2	62.8	15.3	10.8	1.04
150 minutes	0.96	80.9	4.2	55.0	5	8	68.8	86.4	59.4	14.5	10.0	
B. S., 25 Ht., 157.7 Cm. Wt., 48.9 Kg. Dose of glucose, 80 Gm.												
Basal	0.81	68.1	0	46.5	0	0	57.9	35.4	20.5	5.0	...	1.12
Post glucose:												
30 minutes	0.88	71.9	3.8	48.9	5	6	61.1	59.2	36.2	8.8	3.8	1.74†
60 minutes	0.92	70.1	2.0	47.7	3	2	59.6	72.8	43.4	10.6	5.6	2.1
90 minutes	0.97	68.8	0.7	46.8	1	1	58.5	89.8	52.5	12.8	7.8	
120 minutes	0.95	67.7	−0.4	46.0	−1	−1	57.5	83.0	47.7	11.6	6.6	1.4
150 minutes	0.96	63.5	−4.6	43.2	−7	−9	54.0	86.4	46.7	11.4	6.4	
E. R., 36 Ht., 168 Cm. Wt., 62.1 Kg. Dose of glucose, 100 Gm.												
Basal	0.72	90.5	0	57.9	0	0	84.6	4.8	4.1	1.0	...	0.94
Post glucose:												
30 minutes	0.76	104.0	4.5	60.5	4	7	88.4	18.4	16.3	4.0	3.0	1.3†
60 minutes	0.835	100.4	0.9	58.4	1	1	85.4	43.9	37.5	9.2	8.2	1.5
90 minutes	0.85	116.5	17.0	67.7	17	25	99.0	49.0	48.5	11.8	10.8	
120 minutes	0.92	96.5	−3.0	56.1	−3	−5	82.0	72.8	59.6	14.5	13.5	1.07
150 minutes	0.89	100.6	1.1	58.5	1	2	85.5	62.6	53.5	13.0	12.0	

* 15 per cent. deducted from calories per hour for calories from (nitrogen) protein.
† Blood sugar 15 minutes post glucose.

TABLE 7.—Grams of Carbohydrate Utilized by Normal Controls

	Name										Average
	C.L.	H.D.	W.V.G.	F.H.	B.S.	M.C.	M.C.	H.J.	R.Mc.	H.R.G.	
Total gm. carbohydrate utilized in 2½ hours	19.5	19.9	24.6	17.6	14.6	17.4	18.5	21.4	25.0	15.9	19.4
Dose of glucose, gm.	114	120	126	91	90	89	95	110	137	100	
Percentage of dose utilized	17.1	16.6	19.5	19.3	16.2	19.6	19.5	19.5	18.3	15.9	18.1

fed rats on high carbohydrate diets had negligible amounts of glycogen stored in their livers, while control animals on the same diet showed large amounts. There is also some clinical evidence that points to the lack of glycogen reserve in hyperthyroidism. It has been observed that subjects with exophthalmic goiter can be sent into acidosis very easily by brief periods of fasting. A very striking example of this was seen.[5] The patient entered the hospital for the treatment of hyperthyroidism. As she had a glycosuria on general diet she was put on the "standard strict diet" (approximately 10 gm. carbohydrate; 100 gm. protein; 100 gm. fat) in an attempt to clear up the glycosuria. She gradually went into acidosis. This was soon cleared up under carbohydrate feeding. The carbohydrate in the diet was then rapidly increased until 190 gm. were given per day without appreciable quantitative change in the glycosuria. A subsequent diet with restricted carbohydrate promptly brought on an acidosis with impending coma, which was quickly cleared up by carbohydrate feeding. This suggests that the patient had a very small glycogen reserve.

TABLE 8.—GRAMS OF CARBOHYDRATE UTILIZED BY SUBJECTS WITH HYPERTHYROIDISM

	Name										Average
	F.B.	H.G.	F.K.	C.E.	L.M.	A.S.	M.D.	G.S.	B.S.	E.R.	
Total gm. carbohydrate utilized in 2½ hours.....	38.6	27.0	22.7	38.0	36.3	23.9	38.3	33.0	27.6	26.2	31.2
Dose of glucose, gm.....	94	84	65	92	82	72	100	88	86	100	
Percentage of dose utilized.....	41.1	32.2	34.9	41.3	44.3	33.2	38.3	37.5	32.1	26.2	36.1

SUMMARY

Ten normal persons and ten subjects with exophthalmic goiter have been studied under identical conditions. The blood sugar curves in the control cases were entirely normal, while those in the cases of hyperthyroidism, for the most part, showed the usual variation, i. e., an abnormally high peak maintained over a prolonged period. The respiratory quotients in the normal cases revealed normal carbohydrate storage and response while those in the cases of hyperthyroidism showed a greater and more rapid rise, which made for a striking increase in the carbohydrate utilization.

CONCLUSIONS

1. The abnormal blood sugar curves reported heretofore in cases of hyperthyroidism were found, for the most part, in our cases. Normal curves in strikingly toxic cases, however, were not unusual.

5. Presbyterian Hospital Surgical Service, History 30699.

2. It has been shown that in hyperthyroidism, sugar, when it is offered to the tissues as a fuel, is burned with great avidity. The increased utilization of carbohydrate after carbohydrate ingestion, along with the maintained high blood sugar, points toward an inability to store glucose—most probably a failure of liver storage, due to some toxic change in the liver caused by the disease. This fits in with the results found in thyroid fed animals, and is suggested by clinical cases of exophthalmic goiter in which carbohydrate restriction is attempted.

BOOK REVIEWS

THE PRINCIPLES OF THERAPEUTICS. By Oliver T. Osborne, M.A., M.D., Professor of Therapeutics, Department of Medicine, Yale University. Pp. 881. Philadelphia and London: W. B. Saunders Company, 1921

It is, perhaps, somewhat of a surprise, certainly a pleasure, to open a textbook, entitled "The Principles of Therapeutics," and discover that only about two thirds of the text is devoted to drug therapy, while the remainder presents a consideration of therapeutic measures which are not dependent essentially on the administration of drugs The book is intended to give the advanced student the data which he must necessarily know in order to understand the objects of scientific treatment of disease, but the plan is admittedly comprehensive and it is only by condensation and concentration that it is possible to include such a wide field in a textbook of 835 pages.

An attempt has been made to present the subject in as practical a manner as possible. The book is divided into fifteen parts, with several sections. Part I considers the art of writing prescriptions. Part II is devoted to a description of the valuable drugs and preparations of the United States Pharmacopeia with comments. Part III considers useful drugs classified according to their therapeutic action. Part IV is devoted to endocrine glands and organotherapy. Part V to practical therapeutic measures. Part VI to the use of vaccines and serums. Part VII to foods and diets. Part VIII to general physical measures. Part IX to chronic drug poisoning. Part X to industrial poisoning. Part XI to the treatment of emergencies. Part XII to the treatment of simple disturbances of the surface of the body. Part XIII to practical advice to young physicians. Part XIV to medical laws and departments of health, and Part XV to medical ethics.

The object is a worthy one but the value of the book obviously depends upon the intelligent selection of subjects for discussion and on the skill with which the relative value of different therapeutic measures is emphasized.

Part III, dealing with drug therapy, is arranged in somewhat the same manner as the therapeutic index of the valuable little volume called "Useful Drugs," published by the American Medical Association, which has its practical advantages particularly when one may go to a standard textbook on pharmacology for descriptions of drugs that are classified in the more usual manner. In reviewing this section, however, one cannot help but feel that the 280 pages devoted to it might have been enlarged with some value and at the expense of Part IV in which 112 pages are devoted to endocrine glands and organotherapy. Particularly the latter part of this section, which presents a description of the physiologic action of the prostate, thymus, pineal gland, the pancreas, spleen, liver, kidneys, parotid gland, brain, lymph nodes and bone marrow, might well have been omitted. The attempt which is made to describe the important features of modern therapy which come within the scope of the other parts of this book, is praiseworthy, but the field is so wide and the discussions on such important therapeutic measures as foods and diets and of physical methods has necessarily to be made so short that they scarcely attain their object and it is dubious whether anyone who goes to this section for information as regards the use of these measures can find more than a general statement as to their relative value and importance. Indeed he would usually have to seek further to find directions for putting them into effect. Though, therefore, at first sight the titles of these parts indicate a text of considerable practical value, one finds on careful reading that the information is only of a general nature and the concise directions which are necessary to employ many methods that are undoubtedly of considerable practical importance, are omitted.

This book can be employed, therefore, to good advantage for obtaining specific information concerning the action and use of a limited number of drugs and for general information concerning the relative value of various other therapeutic measures in the treatment of disease.

PROTEIN THERAPY AND NONSPECIFIC RESISTANCE. By WILLIAM F. PETERSEN, M.D., Associate in Pathology, University of Illinois, College of Medicine, Chicago. With an introduction by JOSEPH L. MILLER, M.D., Professor of Medicine, Rush Medical College, University of Chicago, Chicago. Pp. 314. New York: The Macmillan Company, 1922

When one reads a book such as this, he is impressed with the great desirability of arranging some method of printing comparatively inexpensive paper bound monographs on subjects which are too new to be incorporated in a textbook and systems of medicine, and yet which through publication in medical journals are attracting general interest. A book of any size devoted to such topics, no matter how carefully prepared, rapidly becomes out of date and must be followed by a second edition or a second book which presents the subject in a more advanced stage of its development. The value of such monographs, therefore, is temporary and it should be possible to publish them as such in a readily accessible, inexpensive form.

Dr. Petersen, in this book, covers the existing knowledge concerning protein therapy and nonspecific resistance in a thorough and comprehensive manner, and one can find in this volume of 314 pages, reference to practically all the work which up to the present time has been done on this subject or has been published in closely allied fields. It is only necessary to state that the bibliography covers about fifty pages in order to give one an idea of the thoroughness with which the subject is reviewed As is quite natural with one who has produced so much in this particular field, one finds an indication throughout the book of the author's interest in the subject and his enthusiasm for the practical importance of this method of treatment, and in Chapters V and VI in which he discusses "theories concerning the mechanism of the reaction" and "the probable mechanism of the reaction," he devotes considerable space to the development of hypotheses and theories for which he himself is, in part, responsible.

In places, one is inclined to take exception to a somewhat uncritical presentation of the literature on this general subject and at times the rather unfortunate impression is produced that the author accepts in equally good faith the results of investigations made by men whose work has and has not been generally confirmed. Undoubtedly, however, this book should attract a well deserved attention, for it presents in very complete form a subject about which it is difficult, without consulting a very large bibliography, to obtain any accurate information, and at the same time offers in very interesting form the author's own views as regards the theoretic action of nonspecific protein therapy and resistance.